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~~*CORYNEBACTERIUM GLUTAMICUM* GENES ENCODING PROTEINS INVOLVED IN CARBON METABOLISM AND ENERGY PRODUCTION~~

Related Applications

This application claims priority to prior U.S. Provisional Patent Application Serial No. 60/141031, filed June 25, 1999, U.S. Provisional Patent Application Serial No. 60/143208, filed July 9, 1999, and U.S. Provisional Patent Application Serial No. 60/151572, filed August 31, 1999. This application also claims priority to prior German Patent Application No. 19931412.8, filed July 8, 1999, German Patent Application No. 19931413.6, filed July 8, 1999, German Patent Application No. 19931419.5, filed July 8, 1999, German Patent Application No. 19931420.9, filed July 8, 1999, German Patent Application No. 19931424.1, filed July 8, 1999, German Patent Application No. 19931428.4 , filed July 8, 1999, German Patent Application No. 19931431.4, filed July 8, 1999, German Patent Application No. 19931433.0, filed July 8, 1999, German Patent Application No. 19931434.9, filed July 8, 1999, German Patent Application No. 19931510.8, filed July 8, 1999, German Patent Application No. 19931562.0, filed July 8, 1999, German Patent Application No. 19931634.1, filed July 8, 1999, German Patent Application No. 19932180.9, filed July 9, 1999, German Patent Application No. 19932227.9, filed July 9, 1999, German Patent Application No. 19932230.9, filed July 9, 1999, German Patent Application No. 19932924.9, filed July 14, 1999, German Patent Application No. 19932973.7, filed July 14, 1999, German Patent Application No. 19933005.0, filed July 14, 1999, German Patent Application No. 19940765.7, filed August 27, 1999, German Patent Application No. 19942076.9, filed September 3, 1999, German Patent Application No. 19942079.3, filed September 3, 1999, German Patent Application No. 19942086.6, filed September 3, 1999, German Patent Application No. 19942087.4, filed September 3, 1999, German Patent Application No. 19942088.2, filed September 3, 1999, German Patent Application No. 19942095.5, filed September 3, 1999, German Patent Application No. 19942123.4, filed September 3, 1999, and German Patent Application No. 19942125.0, filed September 3, 1999. The entire contents of all of the aforementioned application are hereby expressly incorporated herein by this reference.

Background of the Invention

Certain products and by-products of naturally-occurring metabolic processes in cells have utility in a wide array of industries, including the food, feed, cosmetics, and pharmaceutical industries. These molecules, collectively termed 'fine chemicals', include organic acids, both proteinogenic and non-proteinogenic amino acids,

nucleotides and nucleosides, lipids and fatty acids, diols, carbohydrates, aromatic compounds, vitamins and cofactors, and enzymes. Their production is most conveniently performed through the large-scale culture of bacteria developed to produce and secrete large quantities of one or more desired molecules. One particularly useful organism for this purpose is *Corynebacterium glutamicum*, a gram positive, nonpathogenic bacterium. Through strain selection, a number of mutant strains have been developed which produce an array of desirable compounds. However, selection of strains improved for the production of a particular molecule is a time-consuming and difficult process.

Summary of the Invention

The invention provides novel bacterial nucleic acid molecules which have a variety of uses. These uses include the identification of microorganisms which can be used to produce fine chemicals, the modulation of fine chemical production in *C. glutamicum* or related bacteria, the typing or identification of *C. glutamicum* or related bacteria, as reference points for mapping the *C. glutamicum* genome, and as markers for transformation. These novel nucleic acid molecules encode proteins, referred to herein as sugar metabolism and oxidative phosphorylation (SMP) proteins.

C. glutamicum is a gram positive, aerobic bacterium which is commonly used in industry for the large-scale production of a variety of fine chemicals, and also for the degradation of hydrocarbons (such as in petroleum spills) and for the oxidation of terpenoids. The SMP nucleic acid molecules of the invention, therefore, can be used to identify microorganisms which can be used to produce fine chemicals, *e.g.*, by fermentation processes. Modulation of the expression of the SMP nucleic acids of the invention, or modification of the sequence of the SMP nucleic acid molecules of the invention, can be used to modulate the production of one or more fine chemicals from a microorganism (*e.g.*, to improve the yield or production of one or more fine chemicals from a Corynebacterium or Brevibacterium species).

The SMP nucleic acids of the invention may also be used to identify an organism as being *Corynebacterium glutamicum* or a close relative thereof, or to identify the presence of *C. glutamicum* or a relative thereof in a mixed population of microorganisms. The invention provides the nucleic acid sequences of a number of *C. glutamicum* genes; by probing the extracted genomic DNA of a culture of a unique or mixed population of microorganisms under stringent conditions with a probe spanning a region of a *C. glutamicum* gene which is unique to this organism, one can ascertain whether this organism is present. Although *Corynebacterium glutamicum* itself is nonpathogenic, it is related to species pathogenic in humans, such as *Corynebacterium*

diphtheriae (the causative agent of diphtheria); the detection of such organisms is of significant clinical relevance.

The SMP nucleic acid molecules of the invention may also serve as reference points for mapping of the *C. glutamicum* genome, or of genomes of related organisms. Similarly, these molecules, or variants or portions thereof, may serve as markers for genetically engineered Corynebacterium or Brevibacterium species.

e.g.e.g. The SMP proteins encoded by the novel nucleic acid molecules of the invention are capable of, for example, performing a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. Given the availability of cloning vectors for use in *Corynebacterium glutamicum*, such as those disclosed in Sinskey *et al.*, U.S. Patent No. 4,649,119, and techniques for genetic manipulation of *C. glutamicum* and the related *Brevibacterium* species (*e.g.*, *lactofermentum*) (Yoshihama et al, *J. Bacteriol.* 162: 591-597 (1985); Katsumata *et al.*, *J. Bacteriol.* 159: 306-311 (1984); and Santamaria *et al.*, *J. Gen. Microbiol.* 130: 2237-2246 (1984)), the nucleic acid molecules of the invention may be utilized in the genetic engineering of this organism to make it a better or more efficient producer of one or more fine chemicals. This improved production or efficiency of production of a fine chemical may be due to a direct effect of manipulation of a gene of the invention, or it may be due to an indirect effect of such manipulation.

There are a number of mechanisms by which the alteration of an SMP protein of the invention may directly affect the yield, production, and/or efficiency of production of a fine chemical from a *C. glutamicum* strain incorporating such an altered protein. The degradation of high-energy carbon molecules such as sugars, and the conversion of compounds such as NADH and $FADH_2$ to compounds containing high energy phosphate bonds via oxidative phosphorylation results in a number of compounds which themselves may be desirable fine chemicals, such as pyruvate, ATP, NADH, and a number of intermediate sugar compounds. Further, the energy molecules (such as ATP) and the reducing equivalents (such as NADH or NADPH) produced by these metabolic pathways are utilized in the cell to drive reactions which would otherwise be energetically unfavorable. Such unfavorable reactions include many biosynthetic pathways for fine chemicals. By improving the ability of the cell to utilize a particular sugar (*e.g.*, by manipulating the genes encoding enzymes involved in the degradation and conversion of that sugar into energy for the cell), one may increase the amount of energy available to permit unfavorable, yet desired metabolic reactions (*e.g.*, the biosynthesis of a desired fine chemical) to occur.

The mutagenesis of one or more SMP genes of the invention may also result in SMP proteins having altered activities which indirectly impact the production of one or more desired fine chemicals from *C. glutamicum*. For example, by increasing the efficiency of utilization of one or more sugars (such that the conversion of the sugar to useful energy molecules is improved), or by increasing the efficiency of conversion of reducing equivalents to useful energy molecules (*e.g.*, by improving the efficiency of oxidative phosphorylation, or the activity of the ATP synthase), one can increase the amount of these high-energy compounds available to the cell to drive normally unfavorable metabolic processes. These processes include the construction of cell walls, transcription, translation, and the biosynthesis of compounds necessary for growth and division of the cells (*e.g.*, nucleotides, amino acids, vitamins, lipids, etc.) (Lengeler *et al.* (1999) Biology of Prokaryotes, Thieme Verlag: Stuttgart, p. 88-109; 913-918; 875-899). By improving the growth and multiplication of these engineered cells, it is possible to increase both the viability of the cells in large-scale culture, and also to improve their rate of division, such that a relatively larger number of cells can survive in fermentor culture. The yield, production, or efficiency of production may be increased, at least due to the presence of a greater number of viable cells, each producing the desired fine chemical. Also, many of the degradation products produced during sugar metabolism are utilized by the cell as precursors or intermediates in the production of other desirable products, such as fine chemicals. So, by increasing the ability of the cell to metabolize sugars, the number of these degradation products available to the cell for other processes should also be increased.

The invention provides novel nucleic acid molecules which encode proteins, referred to herein as SMP proteins, which are capable of, for example, performing a function involved in the metabolism of carbon compounds such as sugars and the generation of energy molecules by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. Nucleic acid molecules encoding an SMP protein are referred to herein as SMP nucleic acid molecules. In a preferred embodiment, the SMP protein participates in the conversion of carbon molecules and degradation products thereof to energy which is utilized by the cell for metabolic processes. Examples of such proteins include those encoded by the genes set forth in Table 1.

Accordingly, one aspect of the invention pertains to isolated nucleic acid molecules (*e.g.*, cDNAs, DNAs, or RNAs) comprising a nucleotide sequence encoding an SMP protein or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection or amplification of SMP-encoding nucleic acid (*e.g.*, DNA or mRNA). In particularly preferred embodiments, the isolated nucleic acid molecule comprises one of the nucleotide sequences set forth in

Appendix A or the coding region or a complement thereof of one of these nucleotide sequences. In other particularly preferred embodiments, the isolated nucleic acid molecule of the invention comprises a nucleotide sequence which hybridizes to or is at least about 50%, preferably at least about 60%, more preferably at least about 70%, 80% or 90%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to a nucleotide sequence set forth in Appendix A, or a portion thereof. In other preferred embodiments, the isolated nucleic acid molecule encodes one of the amino acid sequences set forth in Appendix B. The preferred SMP proteins of the present invention also preferably possess at least one of the SMP activities described herein.

In another embodiment, the isolated nucleic acid molecule encodes a protein or portion thereof wherein the protein or portion thereof includes an amino acid sequence which is sufficiently homologous to an amino acid sequence of Appendix B, *e.g.*, sufficiently homologous to an amino acid sequence of Appendix B such that the protein or portion thereof maintains an SMP activity. Preferably, the protein or portion thereof encoded by the nucleic acid molecule maintains the ability to perform a function involved in the metabolism of carbon compounds such as sugars or the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. In one embodiment, the protein encoded by the nucleic acid molecule is at least about 50%, preferably at least about 60%, and more preferably at least about 70%, 80%, or 90% and most preferably at least about 95%, 96%, 97%, 98%, or 99% or more homologous to an amino acid sequence of Appendix B (*e.g.*, an entire amino acid sequence selected from those sequences set forth in Appendix B). In another preferred embodiment, the protein is a full length *C. glutamicum* protein which is substantially homologous to an entire amino acid sequence of Appendix B (encoded by an open reading frame shown in Appendix A).

In another preferred embodiment, the isolated nucleic acid molecule is derived from *C. glutamicum* and encodes a protein (*e.g.*, an SMP fusion protein) which includes a biologically active domain which is at least about 50% or more homologous to one of the amino acid sequences of Appendix B and is able to perform a function involved in the metabolism of carbon compounds such as sugars or the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*, or has one or more of the activities set forth in Table 1, and which also includes heterologous nucleic acid sequences encoding a heterologous polypeptide or regulatory regions.

In another embodiment, the isolated nucleic acid molecule is at least 15 nucleotides in length and hybridizes under stringent conditions to a nucleic acid

molecule comprising a nucleotide sequence of Appendix A. Preferably, the isolated nucleic acid molecule corresponds to a naturally-occurring nucleic acid molecule. More preferably, the isolated nucleic acid encodes a naturally-occurring *C. glutamicum* SMP protein, or a biologically active portion thereof.

Another aspect of the invention pertains to vectors, *e.g.*, recombinant expression vectors, containing the nucleic acid molecules of the invention, and host cells into which such vectors have been introduced. In one embodiment, such a host cell is used to produce an SMP protein by culturing the host cell in a suitable medium. The SMP protein can be then isolated from the medium or the host cell.

Yet another aspect of the invention pertains to a genetically altered microorganism in which an SMP gene has been introduced or altered. In one embodiment, the genome of the microorganism has been altered by introduction of a nucleic acid molecule of the invention encoding wild-type or mutated SMP sequence as a transgene. In another embodiment, an endogenous SMP gene within the genome of the microorganism has been altered, *e.g.*, functionally disrupted, by homologous recombination with an altered SMP gene. In another embodiment, an endogenous or introduced SMP gene in a microorganism has been altered by one or more point mutations, deletions, or inversions, but still encodes a functional SMP protein. In still another embodiment, one or more of the regulatory regions (*e.g.*, a promoter, repressor, or inducer) of an SMP gene in a microorganism has been altered (*e.g.*, by deletion, truncation, inversion, or point mutation) such that the expression of the SMP gene is modulated. In a preferred embodiment, the microorganism belongs to the genus *Corynebacterium* or *Brevibacterium*, with *Corynebacterium glutamicum* being particularly preferred. In a preferred embodiment, the microorganism is also utilized for the production of a desired compound, such as an amino acid, with lysine being particularly preferred.

In another aspect, the invention provides a method of identifying the presence or activity of *Cornyebacterium diphtheriae* in a subject. This method includes detection of one or more of the nucleic acid or amino acid sequences of the invention (*e.g.*, the sequences set forth in Appendix A or Appendix B) in a subject, thereby detecting the presence or activity of *Corynebacterium diphtheriae* in the subject.

Still another aspect of the invention pertains to an isolated SMP protein or a portion, *e.g.*, a biologically active portion, thereof. In a preferred embodiment, the isolated SMP protein or portion thereof is capable of performing a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. In another preferred embodiment, the isolated SMP

protein or portion thereof is sufficiently homologous to an amino acid sequence of Appendix B such that the protein or portion thereof maintains the ability to perform a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*.

The invention also provides an isolated preparation of an SMP protein. In preferred embodiments, the SMP protein comprises an amino acid sequence of Appendix B. In another preferred embodiment, the invention pertains to an isolated full length protein which is substantially homologous to an entire amino acid sequence of Appendix B (encoded by an open reading frame set forth in Appendix A). In yet another embodiment, the protein is at least about 50%, preferably at least about 60%, and more preferably at least about 70%, 80%, or 90%, and most preferably at least about 95%, 96%, 97%, 98%, or 99% or more homologous to an entire amino acid sequence of Appendix B. In other embodiments, the isolated SMP protein comprises an amino acid sequence which is at least about 50% or more homologous to one of the amino acid sequences of Appendix B and is able to perform a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*, or has one or more of the activities set forth in Table 1.

Alternatively, the isolated SMP protein can comprise an amino acid sequence which is encoded by a nucleotide sequence which hybridizes, *e.g.*, hybridizes under stringent conditions, or is at least about 50%, preferably at least about 60%, more preferably at least about 70%, 80%, or 90%, and even more preferably at least about 95%, 96%, 97%, 98,%, or 99% or more homologous, to a nucleotide sequence of Appendix B. It is also preferred that the preferred forms of SMP proteins also have one or more of the SMP bioactivities described herein.

The SMP polypeptide, or a biologically active portion thereof, can be operatively linked to a non-SMP polypeptide to form a fusion protein. In preferred embodiments, this fusion protein has an activity which differs from that of the SMP protein alone. In other preferred embodiments, this fusion protein performs a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. In particularly preferred embodiments, integration of this fusion protein into a host cell modulates production of a desired compound from the cell.

In another aspect, the invention provides methods for screening molecules which modulate the activity of an SMP protein, either by interacting with the protein itself or a

substrate or binding partner of the SMP protein, or by modulating the transcription or translation of an SMP nucleic acid molecule of the invention.

Another aspect of the invention pertains to a method for producing a fine chemical. This method involves the culturing of a cell containing a vector directing the expression of an SMP nucleic acid molecule of the invention, such that a fine chemical is produced. In a preferred embodiment, this method further includes the step of obtaining a cell containing such a vector, in which a cell is transfected with a vector directing the expression of an SMP nucleic acid. In another preferred embodiment, this method further includes the step of recovering the fine chemical from the culture. In a particularly preferred embodiment, the cell is from the genus *Corynebacterium* or *Brevibacterium*, or is selected from those strains set forth in Table 3.

Another aspect of the invention pertains to methods for modulating production of a molecule from a microorganism. Such methods include contacting the cell with an agent which modulates SMP protein activity or SMP nucleic acid expression such that a cell associated activity is altered relative to this same activity in the absence of the agent. In a preferred embodiment, the cell is modulated for one or more *C. glutamicum* carbon metabolism pathways or for the production of energy through processes such as oxidative phosphorylation, such that the yields or rate of production of a desired fine chemical by this microorganism is improved. The agent which modulates SMP protein activity can be an agent which stimulates SMP protein activity or SMP nucleic acid expression. Examples of agents which stimulate SMP protein activity or SMP nucleic acid expression include small molecules, active SMP proteins, and nucleic acids encoding SMP proteins that have been introduced into the cell. Examples of agents which inhibit SMP activity or expression include small molecules and antisense SMP nucleic acid molecules.

Another aspect of the invention pertains to methods for modulating yields of a desired compound from a cell, involving the introduction of a wild-type or mutant SMP gene into a cell, either maintained on a separate plasmid or integrated into the genome of the host cell. If integrated into the genome, such integration can be random, or it can take place by homologous recombination such that the native gene is replaced by the introduced copy, causing the production of the desired compound from the cell to be modulated. In a preferred embodiment, said yields are increased. In another preferred embodiment, said chemical is a fine chemical. In a particularly preferred embodiment, said fine chemical is an amino acid. In especially preferred embodiments, said amino acid is L-lysine.

Detailed Description of the Invention

The present invention provides SMP nucleic acid and protein molecules which are involved in the metabolism of carbon compounds such as sugars and the generation of energy molecules by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. The molecules of the invention may be utilized in the modulation of production of fine chemicals from microorganisms, such as *C. glutamicum*, either directly (*e.g.*, where overexpression or optimization of a glycolytic pathway protein has a direct impact on the yield, production, and/or efficiency of production of, *e.g.*, pyruvate from modified *C. glutamicum*), or may have an indirect impact which nonetheless results in an increase of yield, production, and/or efficiency of production of the desired compound (*e.g.*, where modulation of proteins involved in oxidative phosphorylation results in alterations in the amount of energy available to perform necessary metabolic processes and other cellular functions, such as nucleic acid and protein biosynthesis and transcription/translation). Aspects of the invention are further explicated below.

I. Fine Chemicals

The term 'fine chemical' is art-recognized and includes molecules produced by an organism which have applications in various industries, such as, but not limited to, the pharmaceutical, agriculture, and cosmetics industries. Such compounds include organic acids, such as tartaric acid, itaconic acid, and diaminopimelic acid, both proteinogenic and non-proteinogenic amino acids, purine and pyrimidine bases, nucleosides, and nucleotides (as described *e.g.* in Kuninaka, A. (1996) Nucleotides and related compounds, p. 561-612, in Biotechnology vol. 6, Rehm *et al.*, eds. VCH: Weinheim, and references contained therein), lipids, both saturated and unsaturated fatty acids (*e.g.*, arachidonic acid), diols (*e.g.*, propane diol, and butane diol), carbohydrates (*e.g.*, hyaluronic acid and trehalose), aromatic compounds (*e.g.*, aromatic amines, vanillin, and indigo), vitamins and cofactors (as described in Ullmann's Encyclopedia of Industrial Chemistry, vol. A27, "Vitamins", p. 443-613 (1996) VCH: Weinheim and references therein; and Ong, A.S., Niki, E. & Packer, L. (1995) "Nutrition, Lipids, Health, and Disease" Proceedings of the UNESCO/Confederation of Scientific and Technological Associations in Malaysia, and the Society for Free Radical Research – Asia, held Sept. 1-3, 1994 at Penang, Malaysia, AOCS Press, (1995)), enzymes, polyketides (Cane *et al.* (1998) *Science* 282: 63-68), and all other chemicals described in Gutcho (1983) Chemicals by Fermentation, Noyes Data Corporation, ISBN: 0818805086 and references therein. The metabolism and uses of certain of these fine chemicals are further explicated below.

A. *Amino Acid Metabolism and Uses*

Amino acids comprise the basic structural units of all proteins, and as such are essential for normal cellular functioning in all organisms. The term "amino acid" is art-recognized. The proteinogenic amino acids, of which there are 20 species, serve as structural units for proteins, in which they are linked by peptide bonds, while the nonproteinogenic amino acids (hundreds of which are known) are not normally found in proteins (see Ulmann's Encyclopedia of Industrial Chemistry, vol. A2, p. 57-97 VCH: Weinheim (1985)). Amino acids may be in the D- or L- optical configuration, though L-amino acids are generally the only type found in naturally-occurring proteins. Biosynthetic and degradative pathways of each of the 20 proteinogenic amino acids have been well characterized in both prokaryotic and eukaryotic cells (see, for example, Stryer, L. Biochemistry, 3rd edition, pages 578-590 (1988)). The 'essential' amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine), so named because they are generally a nutritional requirement due to the complexity of their biosyntheses, are readily converted by simple biosynthetic pathways to the remaining 11 'nonessential' amino acids (alanine, arginine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, and tyrosine). Higher animals do retain the ability to synthesize some of these amino acids, but the essential amino acids must be supplied from the diet in order for normal protein synthesis to occur.

Aside from their function in protein biosynthesis, these amino acids are interesting chemicals in their own right, and many have been found to have various applications in the food, feed, chemical, cosmetics, agriculture, and pharmaceutical industries. Lysine is an important amino acid in the nutrition not only of humans, but also of monogastric animals such as poultry and swine. Glutamate is most commonly used as a flavor additive (mono-sodium glutamate, MSG) and is widely used throughout the food industry, as are aspartate, phenylalanine, glycine, and cysteine. Glycine, L-methionine and tryptophan are all utilized in the pharmaceutical industry. Glutamine, valine, leucine, isoleucine, histidine, arginine, proline, serine and alanine are of use in both the pharmaceutical and cosmetics industries. Threonine, tryptophan, and D/ L-methionine are common feed additives. (Leuchtenberger, W. (1996) Amino aids – technical production and use, p. 466-502 in Rehm *et al.* (eds.) Biotechnology vol. 6, chapter 14a, VCH: Weinheim). Additionally, these amino acids have been found to be useful as precursors for the synthesis of synthetic amino acids and proteins, such as N-acetylcysteine, S-carboxymethyl-L-cysteine, (S)-5-hydroxytryptophan, and others described in Ulmann's Encyclopedia of Industrial Chemistry, vol. A2, p. 57-97, VCH: Weinheim, 1985.

The biosynthesis of these natural amino acids in organisms capable of producing them, such as bacteria, has been well characterized (for review of bacterial amino acid biosynthesis and regulation thereof, see Umbarger, H.E.(1978) *Ann. Rev. Biochem.* 47: 533-606). Glutamate is synthesized by the reductive amination of α-ketoglutarate, an intermediate in the citric acid cycle. Glutamine, proline, and arginine are each subsequently produced from glutamate. The biosynthesis of serine is a three-step process beginning with 3-phosphoglycerate (an intermediate in glycolysis), and resulting in this amino acid after oxidation, transamination, and hydrolysis steps. Both cysteine and glycine are produced from serine; the former by the condensation of homocysteine with serine, and the latter by the transferal of the side-chain β-carbon atom to tetrahydrofolate, in a reaction catalyzed by serine transhydroxymethylase. Phenylalanine, and tyrosine are synthesized from the glycolytic and pentose phosphate pathway precursors erythrose 4-phosphate and phosphoenolpyruvate in a 9-step biosynthetic pathway that differ only at the final two steps after synthesis of prephenate. Tryptophan is also produced from these two initial molecules, but its synthesis is an 11-step pathway. Tyrosine may also be synthesized from phenylalanine, in a reaction catalyzed by phenylalanine hydroxylase. Alanine, valine, and leucine are all biosynthetic products of pyruvate, the final product of glycolysis. Aspartate is formed from oxaloacetate, an intermediate of the citric acid cycle. Asparagine, methionine, threonine, and lysine are each produced by the conversion of aspartate. Isoleucine is formed from threonine. A complex 9-step pathway results in the production of histidine from 5-phosphoribosyl-1-pyrophosphate, an activated sugar.

Amino acids in excess of the protein synthesis needs of the cell cannot be stored, and are instead degraded to provide intermediates for the major metabolic pathways of the cell (for review see Stryer, L. Biochemistry 3rd ed. Ch. 21 "Amino Acid Degradation and the Urea Cycle" p. 495-516 (1988)). Although the cell is able to convert unwanted amino acids into useful metabolic intermediates, amino acid production is costly in terms of energy, precursor molecules, and the enzymes necessary to synthesize them. Thus it is not surprising that amino acid biosynthesis is regulated by feedback inhibition, in which the presence of a particular amino acid serves to slow or entirely stop its own production (for overview of feedback mechanisms in amino acid biosynthetic pathways, see Stryer, L. Biochemistry, 3rd ed. Ch. 24: "Biosynthesis of Amino Acids and Heme" p. 575-600 (1988)). Thus, the output of any particular amino acid is limited by the amount of that amino acid present in the cell.

B. Vitamin, Cofactor, and Nutraceutical Metabolism and Uses

Vitamins, cofactors, and nutraceuticals comprise another group of molecules which the higher animals have lost the ability to synthesize and so must ingest, although they are readily synthesized by other organisms such as bacteria. These molecules are either bioactive substances themselves, or are precursors of biologically active substances which may serve as electron carriers or intermediates in a variety of metabolic pathways. Aside from their nutritive value, these compounds also have significant industrial value as coloring agents, antioxidants, and catalysts or other processing aids. (For an overview of the structure, activity, and industrial applications of these compounds, see, for example, Ullman's Encyclopedia of Industrial Chemistry, "Vitamins" vol. A27, p. 443-613, VCH: Weinheim, 1996.) The term "vitamin" is art-recognized, and includes nutrients which are required by an organism for normal functioning, but which that organism cannot synthesize by itself. The group of vitamins may encompass cofactors and nutraceutical compounds. The language "cofactor" includes nonproteinaceous compounds required for a normal enzymatic activity to occur. Such compounds may be organic or inorganic; the cofactor molecules of the invention are preferably organic. The term "nutraceutical" includes dietary supplements having health benefits in plants and animals, particularly humans. Examples of such molecules are vitamins, antioxidants, and also certain lipids (*e.g.*, polyunsaturated fatty acids).

The biosynthesis of these molecules in organisms capable of producing them, such as bacteria, has been largely characterized (Ullman's Encyclopedia of Industrial Chemistry, "Vitamins" vol. A27, p. 443-613, VCH: Weinheim, 1996; Michal, G. (1999) Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, John Wiley & Sons; Ong, A.S., Niki, E. & Packer, L. (1995) "Nutrition, Lipids, Health, and Disease" Proceedings of the UNESCO/Confederation of Scientific and Technological Associations in Malaysia, and the Society for Free Radical Research – Asia, held Sept. 1-3, 1994 at Penang, Malaysia, AOCS Press: Champaign, IL X, 374 S).

Thiamin (vitamin B_1) is produced by the chemical coupling of pyrimidine and thiazole moieties. Riboflavin (vitamin B_2) is synthesized from guanosine-5'-triphosphate (GTP) and ribose-5'-phosphate. Riboflavin, in turn, is utilized for the synthesis of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The family of compounds collectively termed 'vitamin B_6' (*e.g.*, pyridoxine, pyridoxamine, pyridoxa-5'-phosphate, and the commercially used pyridoxin hydrochloride) are all derivatives of the common structural unit, 5-hydroxy-6-methylpyridine. Pantothenate (pantothenic acid, (R)-(+)-N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine) can be produced either by chemical synthesis or by fermentation. The final steps in pantothenate

biosynthesis consist of the ATP-driven condensation of β-alanine and pantoic acid. The enzymes responsible for the biosynthesis steps for the conversion to pantoic acid, to β-alanine and for the condensation to panthotenic acid are known. The metabolically active form of pantothenate is Coenzyme A, for which the biosynthesis proceeds in 5 enzymatic steps. Pantothenate, pyridoxal-5'-phosphate, cysteine and ATP are the precursors of Coenzyme A. These enzymes not only catalyze the formation of panthothante, but also the production of (R)-pantoic acid, (R)-pantolacton, (R)-panthenol (provitamin B_5), pantetheine (and its derivatives) and coenzyme A.

Biotin biosynthesis from the precursor molecule pimeloyl-CoA in microorganisms has been studied in detail and several of the genes involved have been identified. Many of the corresponding proteins have been found to also be involved in Fe-cluster synthesis and are members of the nifS class of proteins. Lipoic acid is derived from octanoic acid, and serves as a coenzyme in energy metabolism, where it becomes part of the pyruvate dehydrogenase complex and the α-ketoglutarate dehydrogenase complex. The folates are a group of substances which are all derivatives of folic acid, which is turn is derived from L-glutamic acid, p-amino-benzoic acid and 6-methylpterin. The biosynthesis of folic acid and its derivatives, starting from the metabolism intermediates guanosine-5'-triphosphate (GTP), L-glutamic acid and p-amino-benzoic acid has been studied in detail in certain microorganisms.

Corrinoids (such as the cobalamines and particularly vitamin B_{12}) and porphyrines belong to a group of chemicals characterized by a tetrapyrole ring system. The biosynthesis of vitamin B_{12} is sufficiently complex that it has not yet been completely characterized, but many of the enzymes and substrates involved are now known. Nicotinic acid (nicotinate), and nicotinamide are pyridine derivatives which are also termed 'niacin'. Niacin is the precursor of the important coenzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) and their reduced forms.

The large-scale production of these compounds has largely relied on cell-free chemical syntheses, though some of these chemicals have also been produced by large-scale culture of microorganisms, such as riboflavin, Vitamin B_6, pantothenate, and biotin. Only Vitamin B_{12} is produced solely by fermentation, due to the complexity of its synthesis. *In vitro* methodologies require significant inputs of materials and time, often at great cost.

C. Purine, Pyrimidine, Nucleoside and Nucleotide Metabolism and Uses

Purine and pyrimidine metabolism genes and their corresponding proteins are important targets for the therapy of tumor diseases and viral infections. The language

"purine" or "pyrimidine" includes the nitrogenous bases which are constituents of nucleic acids, co-enzymes, and nucleotides. The term "nucleotide" includes the basic structural units of nucleic acid molecules, which are comprised of a nitrogenous base, a pentose sugar (in the case of RNA, the sugar is ribose; in the case of DNA, the sugar is D-deoxyribose), and phosphoric acid. The language "nucleoside" includes molecules which serve as precursors to nucleotides, but which are lacking the phosphoric acid moiety that nucleotides possess. By inhibiting the biosynthesis of these molecules, or their mobilization to form nucleic acid molecules, it is possible to inhibit RNA and DNA synthesis; by inhibiting this activity in a fashion targeted to cancerous cells, the ability of tumor cells to divide and replicate may be inhibited. Additionally, there are nucleotides which do not form nucleic acid molecules, but rather serve as energy stores (*i.e.*, AMP) or as coenzymes (*i.e.*, FAD and NAD).

Several publications have described the use of these chemicals for these medical indications, by influencing purine and/or pyrimidine metabolism (*e.g.* Christopherson, R.I. and Lyons, S.D. (1990) "Potent inhibitors of *de novo* pyrimidine and purine biosynthesis as chemotherapeutic agents." *Med. Res. Reviews* 10: 505-548). Studies of enzymes involved in purine and pyrimidine metabolism have been focused on the development of new drugs which can be used, for example, as immunosuppressants or anti-proliferants (Smith, J.L., (1995) "Enzymes in nucleotide synthesis." *Curr. Opin. Struct. Biol.* 5: 752-757; (1995) *Biochem Soc. Transact.* 23: 877-902). However, purine and pyrimidine bases, nucleosides and nucleotides have other utilities: as intermediates in the biosynthesis of several fine chemicals (*e.g.*, thiamine, S-adenosyl-methionine, folates, or riboflavin), as energy carriers for the cell (*e.g.*, ATP or GTP), and for chemicals themselves, commonly used as flavor enhancers (*e.g.*, IMP or GMP) or for several medicinal applications (see, for example, Kuninaka, A. (1996) Nucleotides and Related Compounds in Biotechnology vol. 6, Rehm *et al.*, eds. VCH: Weinheim, p. 561-612). Also, enzymes involved in purine, pyrimidine, nucleoside, or nucleotide metabolism are increasingly serving as targets against which chemicals for crop protection, including fungicides, herbicides and insecticides, are developed.

The metabolism of these compounds in bacteria has been characterized (for reviews see, for example, Zalkin, H. and Dixon, J.E. (1992) "*de novo* purine nucleotide biosynthesis", in: Progress in Nucleic Acid Research and Molecular Biology, vol. 42, Academic Press:, p. 259-287; and Michal, G. (1999) "Nucleotides and Nucleosides", Chapter 8 in: Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, Wiley: New York). Purine metabolism has been the subject of intensive research, and is essential to the normal functioning of the cell. Impaired purine metabolism in higher animals can cause severe disease, such as gout. Purine nucleotides are synthesized from

ribose-5-phosphate, in a series of steps through the intermediate compound inosine-5'-phosphate (IMP), resulting in the production of guanosine-5'-monophosphate (GMP) or adenosine-5'-monophosphate (AMP), from which the triphosphate forms utilized as nucleotides are readily formed. These compounds are also utilized as energy stores, so their degradation provides energy for many different biochemical processes in the cell. Pyrimidine biosynthesis proceeds by the formation of uridine-5'-monophosphate (UMP) from ribose-5-phosphate. UMP, in turn, is converted to cytidine-5'-triphosphate (CTP). The deoxy- forms of all of these nucleotides are produced in a one step reduction reaction from the diphosphate ribose form of the nucleotide to the diphosphate deoxyribose form of the nucleotide. Upon phosphorylation, these molecules are able to participate in DNA synthesis.

D. Trehalose Metabolism and Uses

Trehalose consists of two glucose molecules, bound in α, α-1,1 linkage. It is commonly used in the food industry as a sweetener, an additive for dried or frozen foods, and in beverages. However, it also has applications in the pharmaceutical, cosmetics and biotechnology industries (see, for example, Nishimoto *et al.*, (1998) U.S. Patent No. 5,759,610; Singer, M.A. and Lindquist, S. (1998) *Trends Biotech.* 16: 460-467; Paiva, C.L.A. and Panek, A.D. (1996) *Biotech. Ann. Rev.* 2: 293-314; and Shiosaka, M. (1997) J. Japan 172: 97-102). Trehalose is produced by enzymes from many microorganisms and is naturally released into the surrounding medium, from which it can be collected using methods known in the art.

II. <u>Sugar and Carbon Molecule Utilization and Oxidative Phosphorylation</u>

Carbon is a critically important element for the formation of all organic compounds, and thus is a nutritional requirement not only for the growth and division of *C. glutamicum*, but also for the overproduction of fine chemicals from this microorganism. Sugars, such as mono-, di-, or polysaccharides, are particularly good carbon sources, and thus standard growth media typically contain one or more of: glucose, fructose, mannose, galactose, ribose, sorbose, ribulose, lactose, maltose, sucrose, raffinose, starch, or cellulose (Ullmann's Encyclopedia of Industrial Chemistry (1987) vol. A9, "Enzymes", VCH: Weinheim). Alternatively, more complex forms of sugar may be utilized in the media, such as molasses, or other by-products of sugar refinement. Other compounds aside from the sugars may be used as alternate carbon sources, including alcohols (*e.g.*, ethanol or methanol), alkanes, sugar alcohols, fatty acids, and organic acids (*e.g.*, acetic acid or lactic acid). For a review of carbon sources and their utilization by microorganisms in culture, see: Ullman's Encyclopedia of

Industrial Chemistry (1987) vol. A9, "Enzymes", VCH: Weinheim; Stoppok, E. and Buchholz, K. (1996) "Sugar-based raw materials for fermentation applications" in Biotechnology (Rehm, H.J. *et al.*, eds.) vol. 6, VCH: Weinheim, p. 5-29; Rehm, H.J. (1980) Industrielle Mikrobiologie, Springer: Berlin; Bartholomew, W.H., and Reiman, H.B. (1979). Economics of Fermentation Processes, in: Peppler, H.J. and Perlman, D., eds. Microbial Technology 2nd ed., vol. 2, chapter 18, Academic Press: New York; and Kockova-Kratachvilova, A. (1981) Characteristics of Industrial Microorganisms, in: Rehm, H.J. and Reed, G., eds. Handbook of Biotechnology, vol. 1, chapter 1, Verlag Chemie: Weinheim.

After uptake, these energy-rich carbon molecules must be processed such that they are able to be degraded by one of the major sugar metabolic pathways. Such pathways lead directly to useful degradation products, such as ribose-5-phosphate and phosphoenolpyruvate, which may be subsequently converted to pyruvate. Three of the most important pathways in bacteria for sugar metabolism include the Embden-Meyerhoff-Pamas (EMP) pathway (also known as the glycolytic or fructose bisphosphate pathway), the hexosemonophosphate (HMP) pathway (also known as the pentose shunt or pentose phosphate pathway), and the Entner-Doudoroff (ED) pathway (for review, see Michal, G. (1999) Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, Wiley: New York, and Stryer, L. (1988) Biochemistry, Chapters 13-19, Freeman: New York, and references therein).

The EMP pathway converts hexose molecules to pyruvate, and in the process produces 2 molecules of ATP and 2 molecules of NADH. Starting with glucose-1-phosphate (which may be either directly taken up from the medium, or alternatively may be generated from glycogen, starch, or cellulose), the glucose molecule is isomerized to fructose-6-phosphate, is phosphorylated, and split into two 3-carbon molecules of glyceraldehyde-3-phosphate. After dehydrogenation, phosphorylation, and successive rearrangements, pyruvate results.

The HMP pathway converts glucose to reducing equivalents, such as NADPH, and produces pentose and tetrose compounds which are necessary as intermediates and precursors in a number of other metabolic pathways. In the HMP pathway, glucose-6-phosphate is converted to ribulose-5-phosphate by two successive dehydrogenase reactions (which also release two NADPH molecules), and a carboxylation step. Ribulose-5-phosphate may also be converted to xyulose-5-phosphate and ribose-5-phosphate; the former can undergo a series of biochemical steps to glucose-6-phosphate, which may enter the EMP pathway, while the latter is commonly utilized as an intermediate in other biosynthetic pathways within the cell.

The ED pathway begins with the compound glucose or gluconate, which is subsequently phosphorylated and dehydrated to form 2-dehydro-3-deoxy-6-P-gluconate. Glucuronate and galacturonate may also be converted to 2-dehydro-3-deoxy-6-P-gluconate through more complex biochemical pathways. This product molecule is subsequently cleaved into glyceraldehyde-3-P and pyruvate; glyceraldehyde-3-P may itself also be converted to pyruvate.

The EMP and HMP pathways share many features, including intermediates and enzymes. The EMP pathway provides the greatest amount of ATP, but it does not produce ribose-5-phosphate, an important precursor for, *e.g.*, nucleic acid biosynthesis, nor does it produce erythrose-4-phosphate, which is important for amino acid biosynthesis. Microorganisms that are capable of using only the EMP pathway for glucose utilization are thus not able to grow on simple media with glucose as the sole carbon source. They are referred to as fastidious organisms, and their growth requires inputs of complex organic compounds, such as those found in yeast extract.

In contrast, the HMP pathway produces all of the precursors necessary for both nucleic acid and amino acid biosynthesis, yet yields only half the amount of ATP energy that the EMP pathway does. The HMP pathway also produces NADPH, which may be used for redox reactions in biosynthetic pathways. The HMP pathway does not directly produce pyruvate, however, and thus these microorganisms must also possess this portion of the EMP pathway. It is therefore not surprising that a number of microorganisms, particularly the facultative anerobes, have evolved such that they possess both of these pathways.

The ED pathway has thus far has only been found in bacteria. Although this pathway is linked partly to the HMP pathway in the reverse direction for precursor formation, the ED pathway directly forms pyruvate by the aldolase cleavage of 3-ketodeoxy-6-phosphogluconate. The ED pathway can exist on its own and is utilized by the majority of strictly aerobic microorganisms. The net result is similar to that of the HMP pathway, although one mole of ATP can be formed only if the carbon atoms are converted into pyruvate, instead of into precursor molecules.

The pyruvate molecules produced through any of these pathways can be readily converted into energy via the Krebs cycle (also known as the citric acid cycle, the citrate cycle, or the tricarboxylic acid cycle (TCA cycle)). In this process, pyruvate is first decarboxylated, resulting in the production of one molecule of NADH, 1 molecule of acetyl-CoA, and 1 molecule of CO_2. The acetyl group of acetyl CoA then reacts with the 4 carbon unit, oxaolacetate, leading to the formation of citric acid, a 6 carbon organic acid. Dehydration and two additional CO_2 molecules are released. Ultimately, oxaloacetate is regenerated and can serve again as an acetyl acceptor, thus completing

the cycle. The electrons released during the oxidation of intermediates in the TCA cycle are transferred to NAD^+ to yield NADH.

During respiration, the electrons from NADH are transferred to molecular oxygen or other terminal electron acceptors. This process is catalyzed by the respiratory chain, an electron transport system containing both integral membrane proteins and membrane associated proteins. This system serves two basic functions: first, to accept electrons from an electron donor and to transfer them to an electron acceptor, and second, to conserve some of the energy released during electron transfer by the synthesis of ATP. Several types of oxidation-reduction enzymes and electron transport proteins are known to be involved in such processes, including the NADH dehydrogenases, flavin-containing electron carriers, iron sulfur proteins, and cytochromes. The NADH dehydrogenases are located at the cytoplasmic surface of the plasma membrane, and transfer hydrogen atoms from NADH to flavoproteins, in turn accepting electrons from NADH. The flavoproteins are a group of electron carriers possessing a flavin prosthetic group which is alternately reduced and oxidized as it accepts and transfers electrons. Three flavins are known to participate in these reactions: riboflavin, flavin-adenine dinucleotide (FAD) and flavin-mononucleotide (FMN). Iron sulfur proteins contain a cluster of iron and sulfur atoms which are not bonded to a heme group, but which still are able to participate in dehydration and rehydration reactions. Succinate dehydrogenase and aconitase are exemplary iron-sulfur proteins; their iron-sulfur complexes serve to accept and transfer electrons as part of the overall electron-transport chain. The cytochromes are proteins containing an iron porphyrin ring (heme). There are a number of different classes of cytochromes, differing in their reduction potentials. Functionally, these cytochromes form pathways in which electrons may be transferred to other cytochromes having increasingly more positive reduction potentials. A further class of non-protein electron carriers is known: the lipid-soluble quinones (*e.g.*, coenzyme Q). These molecules also serve as hydrogen atom acceptors and electron donors.

The action of the respiratory chain generates a proton gradient across the cell membrane, resulting in proton motive force. This force is utilized by the cell to synthesize ATP, via the membrane-spanning enzyme, ATP synthase. This enzyme is a multiprotein complex in which the transport of H^+ molecules through the membrane results in the physical rotation of the intracellular subunits and concomitant phosphorylation of ADP to form ATP (for review, see Fillingame, R.H. and Divall, S. (1999) *Novartis Found. Symp.* 221: 218-229, 229-234).

Non-hexose carbon substrates may also serve as carbon and energy sources for cells. Such substrates may first be converted to hexose sugars in the gluconeogenesis

pathway, where glucose is first synthesized by the cell and then is degraded to produce energy. The starting material for this reaction is phosphoenolpyruvate (PEP), which is one of the key intermediates in the glycolytic pathway. PEP may be formed from substrates other than sugars, such as acetic acid, or by decarboxylation of oxaloacetate (itself an intermediate in the TCA cycle). By reversing the glycolytic pathway (utilizing a cascade of enzymes different than those of the original glycolysis pathway), glucose-6-phosphate may be formed. The conversion of pyruvate to glucose requires the utilization of 6 high energy phosphate bonds, whereas glycolysis only produces 2 ATP in the conversion of glucose to pyruvate. However, the complete oxidation of glucose (glycolysis, conversion of pyruvate into acetyl CoA, citric acid cycle, and oxidative phosphorylation) yields between 36-38 ATP, so the net loss of high energy phosphate bonds experienced during gluconeogenesis is offset by the overall greater gain in such high-energy molecules produced by the oxidation of glucose.

III. Elements and Methods of the Invention

The present invention is based, at least in part, on the discovery of novel molecules, referred to herein as SMP nucleic acid and protein molecules, which participate in the conversion of sugars to useful degradation products and energy (*e.g.*, ATP) in *C. glutamicum* or which may participate in the production of useful energy-rich molecules (*e.g.*, ATP) by other processes, such as oxidative phosphorylation. In one embodiment, the SMP molecules participate in the metabolism of carbon compounds such as sugars or the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. In a preferred embodiment, the activity of the SMP molecules of the present invention to contribute to carbon metabolism or energy production in *C. glutamicum* has an impact on the production of a desired fine chemical by this organism. In a particularly preferred embodiment, the SMP molecules of the invention are modulated in activity, such that the *C. glutamicum* metabolic and energetic pathways in which the SMP proteins of the invention participate are modulated in yield, production, and/or efficiency of production, which either directly or indirectly modulates the yield, production, and/or efficiency of production of a desired fine chemical by *C. glutamicum*.

The language, "SMP protein" or "SMP polypeptide" includes proteins which are capable of performing a function involved in the metabolism of carbon compounds such as sugars and the generation of energy molecules by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. Examples of SMP proteins include those encoded by the SMP genes set forth in Table 1 and Appendix A. The terms "SMP gene" or "SMP nucleic acid sequence" include nucleic acid sequences encoding an SMP

protein, which consist of a coding region and also corresponding untranslated 5' and 3' sequence regions. Examples of SMP genes include those set forth in Table 1. The terms "production" or "productivity" are art-recognized and include the concentration of the fermentation product (for example, the desired fine chemical) formed within a given time and a given fermentation volume (*e.g.*, kg product per hour per liter). The term "efficiency of production" includes the time required for a particular level of production to be achieved (for example, how long it takes for the cell to attain a particular rate of output of a fine chemical). The term "yield" or "product/carbon yield" is art-recognized and includes the efficiency of the conversion of the carbon source into the product (*i.e.*, fine chemical). This is generally written as, for example, kg product per kg carbon source. By increasing the yield or production of the compound, the quantity of recovered molecules, or of useful recovered molecules of that compound in a given amount of culture over a given amount of time is increased. The terms "biosynthesis" or a "biosynthetic pathway" are art-recognized and include the synthesis of a compound, preferably an organic compound, by a cell from intermediate compounds in what may be a multistep and highly regulated process. The terms "degradation" or a "degradation pathway" are art-recognized and include the breakdown of a compound, preferably an organic compound, by a cell to degradation products (generally speaking, smaller or less complex molecules) in what may be a multistep and highly regulated process. The term "degradation product" is art-recognized and includes breakdown products of a compound. Such products may themselves have utility as precursor (starting point) or intermediate molecules necessary for the biosynthesis of other compounds by the cell. The language "metabolism" is art-recognized and includes the totality of the biochemical reactions that take place in an organism. The metabolism of a particular compound, then, (*e.g.*, the metabolism of an amino acid such as glycine) comprises the overall biosynthetic, modification, and degradation pathways in the cell related to this compound.

In another embodiment, the SMP molecules of the invention are capable of modulating the production of a desired molecule, such as a fine chemical, in a microorganism such as *C. glutamicum*. There are a number of mechanisms by which the alteration of an SMP protein of the invention may directly affect the yield, production, and/or efficiency of production of a fine chemical from a *C. glutamicum* strain incorporating such an altered protein. The degradation of high-energy carbon molecules such as sugars, and the conversion of compounds such as NADH and $FADH_2$ to more useful forms via oxidative phosphorylation results in a number of compounds which themselves may be desirable fine chemicals, such as pyruvate, ATP, NADH, and a number of intermediate sugar compounds. Further, the energy molecules (such as

ATP) and the reducing equivalents (such as NADH or NADPH) produced by these metabolic pathways are utilized in the cell to drive reactions which would otherwise be energetically unfavorable. Such unfavorable reactions include many biosynthetic pathways for fine chemicals. By improving the ability of the cell to utilize a particular sugar (*e.g.*, by manipulating the genes encoding enzymes involved in the degradation and conversion of that sugar into energy for the cell), one may increase the amount of energy available to permit unfavorable, yet desired metabolic reactions (*e.g.*, the biosynthesis of a desired fine chemical) to occur.

The mutagenesis of one or more SMP genes of the invention may also result in SMP proteins having altered activities which indirectly impact the production of one or more desired fine chemicals from *C. glutamicum*. For example, by increasing the efficiency of utilization of one or more sugars (such that the conversion of the sugar to useful energy molecules is improved), or by increasing the efficiency of conversion of reducing equivalents to useful energy molecules (*e.g.*, by improving the efficiency of oxidative phosphorylation, or the activity of the ATP synthase), one can increase the amount of these high-energy compounds available to the cell to drive normally unfavorable metabolic processes. These processes include the construction of cell walls, transcription, translation, and the biosynthesis of compounds necessary for growth and division of the cells (*e.g.*, nucleotides, amino acids, vitamins, lipids, etc.) (Lengeler *et al.* (1999) Biology of Prokaryotes, Thieme Verlag: Stuttgart, p. 88-109; 913-918; 875-899). By improving the growth and multiplication of these engineered cells, it is possible to increase both the viability of the cells in large-scale culture, and also to improve their rate of division, such that a relatively larger number of cells can survive in fermentor culture. The yield, production, or efficiency of production may be increased, at least due to the presence of a greater number of viable cells, each producing the desired fine chemical. Further, a number of the degradation and intermediate compounds produced during sugar metabolism are necessary precursors and intermediates for other biosynthetic pathways throughout the cell. For example, many amino acids are synthesized directly from compounds normally resulting from glycolysis or the TCA cycle (*e.g.*, serine is synthesized from 3-phosphoglycerate, an intermediate in glycolysis). Thus, by increasing the efficiency of conversion of sugars to useful energy molecules, it is also possible to increase the amount of useful degradation products as well.

The isolated nucleic acid sequences of the invention are contained within the genome of a *Corynebacterium glutamicum* strain available through the American Type Culture Collection, given designation ATCC 13032. The nucleotide sequence of the isolated *C. glutamicum* SMP DNAs and the predicted amino acid sequences of the *C.*

glutamicum SMP proteins are shown in Appendices A and B, respectively. Computational analyses were performed which classified and/or identified these nucleotide sequences as sequences which encode proteins having a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*.

The present invention also pertains to proteins which have an amino acid sequence which is substantially homologous to an amino acid sequence of Appendix B. As used herein, a protein which has an amino acid sequence which is substantially homologous to a selected amino acid sequence is least about 50% homologous to the selected amino acid sequence, *e.g.*, the entire selected amino acid sequence. A protein which has an amino acid sequence which is substantially homologous to a selected amino acid sequence can also be least about 50-60%, preferably at least about 60-70%, and more preferably at least about 70-80%, 80-90%, or 90-95%, and most preferably at least about 96%, 97%, 98%, 99% or more homologous to the selected amino acid sequence.

An SMP protein or a biologically active portion or fragment thereof of the invention can participate in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*, or can have one or more of the activities set forth in Table 1.

Various aspects of the invention are described in further detail in the following subsections:

A. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode SMP polypeptides or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes or primers for the identification or amplification of SMP-encoding nucleic acid (*e.g.*, SMP DNA). As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. This term also encompasses untranslated sequence located at both the 3' and 5' ends of the coding region of the gene: at least about 100 nucleotides of sequence upstream from the 5' end of the coding region and at least about 20 nucleotides of sequence downstream from the 3'end of the coding region of the gene. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA. An "isolated" nucleic acid molecule is one which is separated

from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated SMP nucleic acid molecule can contain less than about 5 kb, 4kb, 3kb, 2kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived (e.g, a *C. glutamicum* cell). Moreover, an "isolated" nucleic acid molecule, such as a DNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having a nucleotide sequence of Appendix A, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. For example, a *C. glutamicum* SMP DNA can be isolated from a *C. glutamicum* library using all or portion of one of the sequences of Appendix A as a hybridization probe and standard hybridization techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). Moreover, a nucleic acid molecule encompassing all or a portion of one of the sequences of Appendix A can be isolated by the polymerase chain reaction using oligonucleotide primers designed based upon this sequence (*e.g.*, a nucleic acid molecule encompassing all or a portion of one of the sequences of Appendix A can be isolated by the polymerase chain reaction using oligonucleotide primers designed based upon this same sequence of Appendix A). For example, mRNA can be isolated from normal endothelial cells (*e.g.*, by the guanidinium-thiocyanate extraction procedure of Chirgwin *et al.* (1979) *Biochemistry* 18: 5294-5299) and DNA can be prepared using reverse transcriptase (*e.g.*, Moloney MLV reverse transcriptase, available from Gibco/BRL, Bethesda, MD; or AMV reverse transcriptase, available from Seikagaku America, Inc., St. Petersburg, FL). Synthetic oligonucleotide primers for polymerase chain reaction amplification can be designed based upon one of the nucleotide sequences shown in Appendix A. A nucleic acid of the invention can be amplified using cDNA or, alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to an SMP nucleotide sequence can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In a preferred embodiment, an isolated nucleic acid molecule of the invention comprises one of the nucleotide sequences shown in Appendix A. The sequences of Appendix A correspond to the *Corynebacterium glutamicum* SMP DNAs of the invention. This DNA comprises sequences encoding SMP proteins (*i.e.*, the "coding region", indicated in each sequence in Appendix A), as well as 5' untranslated sequences and 3' untranslated sequences, also indicated in Appendix A. Alternatively, the nucleic acid molecule can comprise only the coding region of any of the sequences in Appendix A.

For the purposes of this application, it will be understood that each of the sequences set forth in Appendix A has an identifying RXA, RXN, or RXS number having the designation "RXA," "RXN," or "RXS" followed by 5 digits (*i.e.*, RXA00013,RXN00043, or RXS0735). Each of these sequences comprises up to three parts: a 5' upstream region, a coding region, and a downstream region. Each of these three regions is identified by the same RXA, RXN, or RXS designation to eliminate confusion. The recitation "one of the sequences in Appendix A", then, refers to any of the sequences in Appendix A, which may be distinguished by their differing RXA, RXN, or RXS designations. The coding region of each of these sequences is translated into a corresponding amino acid sequence, which is set forth in Appendix B. The sequences of Appendix B are identified by the same RXA, RXN, or RXS designations as Appendix A, such that they can be readily correlated. For example, the amino acid sequence in Appendix B designated RXA00013 is a translation of the coding region of the nucleotide sequence of nucleic acid molecule RXA00013 in Appendix A, and the amino acid sequence in Appendix B designated RXN00043 is a translation of the coding region of the nucleotide sequence of nucleic acid molecule RXN00043 in Appendix A. Each of the RXARXN and RXS nucleotide and amino acid sequences of the invention has also been assigned a SEQ ID NO, as indicated in Table 1.

Several of the genes of the invention are "F-designated genes". An F-designated gene includes those genes set forth in Table 1 which have an 'F' in front of the RXAdesignation. For example, SEQ ID NO:11, designated, as indicated on Table 1, as "F RXA01312", is an F-designated gene, as are SEQ ID NOs: 29, 33, and 39 (designated on Table 1 as "F RXA02803", "F RXA02854", and "F RXA01365", respectively).

In one embodiment, the nucleic acid molecules of the present invention are not intended to include those compiled in Table 2. In the case of the dapD gene, a sequence for this gene was published in Wehrmann, A., *et al.* (1998) *J. Bacteriol.* 180(12): 3159-3165. However, the sequence obtained by the inventors of the present application is significantly longer than the published version. It is believed that the published version

relied on an incorrect start codon, and thus represents only a fragment of the actual coding region.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of one of the nucleotide sequences shown in Appendix A, or a portion thereof. A nucleic acid molecule which is complementary to one of the nucleotide sequences shown in Appendix A is one which is sufficiently complementary to one of the nucleotide sequences shown in Appendix A such that it can hybridize to one of the nucleotide sequences shown in Appendix A, thereby forming a stable duplex.

In still another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleotide sequence which is at least about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to a nucleotide sequence shown in Appendix A, or a portion thereof. Ranges and identity values intermediate to the above-recited ranges, (*e.g.*, 70-90% identical or 80-95% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included. In an additional preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleotide sequence which hybridizes, *e.g.*, hybridizes under stringent conditions, to one of the nucleotide sequences shown in Appendix A, or a portion thereof.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the coding region of one of the sequences in Appendix A, for example a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of an SMP protein. The nucleotide sequences determined from the cloning of the SMP genes from *C. glutamicum* allows for the generation of probes and primers designed for use in identifying and/or cloning SMP homologues in other cell types and organisms, as well as SMP homologues from other *Corynebacteria* or related species. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 40, 50 or 75 consecutive nucleotides of a sense strand of one of the sequences set forth in Appendix A, an anti-sense sequence of one of the sequences set forth in Appendix A, or naturally occurring mutants thereof. Primers based on a nucleotide

sequence of Appendix A can be used in PCR reactions to clone SMP homologues. Probes based on the SMP nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.* the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells which misexpress an SMP protein, such as by measuring a level of an SMP-encoding nucleic acid in a sample of cells, *e.g.*, detecting SMP mRNA levels or determining whether a genomic SMP gene has been mutated or deleted.

In one embodiment, the nucleic acid molecule of the invention encodes a protein or portion thereof which includes an amino acid sequence which is sufficiently homologous to an amino acid sequence of Appendix B such that the protein or portion thereof maintains the ability to perform a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. As used herein, the language "sufficiently homologous" refers to proteins or portions thereof which have amino acid sequences which include a minimum number of identical or equivalent (*e.g.*, an amino acid residue which has a similar side chain as an amino acid residue in one of the sequences of Appendix B) amino acid residues to an amino acid sequence of Appendix B such that the protein or portion thereof is able to perform a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. Protein members of such sugar metabolic pathways or energy producing systems, as described herein, may play a role in the production and secretion of one or more fine chemicals. Examples of such activities are also described herein. Thus, "the function of an SMP protein" contributes either directly or indirectly to the yield, production, and/or efficiency of production of one or more fine chemicals. Examples of SMP protein activities are set forth in Table 1.

In another embodiment, the protein is at least about 50-60%, preferably at least about 60-70%, and more preferably at least about 70-80%, 80-90%, 90-95%, and most preferably at least about 96%, 97%, 98%, 99% or more homologous to an entire amino acid sequence of Appendix B.

Portions of proteins encoded by the SMP nucleic acid molecules of the invention are preferably biologically active portions of one of the SMP proteins. As used herein, the term "biologically active portion of an SMP protein" is intended to include a portion, *e.g.*, a domain/motif, of an SMP protein that participates in the metabolism of carbon compounds such as sugars, or in energy-generating pathways in *C. glutamicum*, or has

an activity as set forth in Table 1. To determine whether an SMP protein or a biologically active portion thereof can participate in the metabolism of carbon compounds or in the production of energy-rich molecules in *C. glutamicum*, an assay of enzymatic activity may be performed. Such assay methods are well known to those of ordinary skill in the art, as detailed in Example 8 of the Exemplification.

Additional nucleic acid fragments encoding biologically active portions of an SMP protein can be prepared by isolating a portion of one of the sequences in Appendix B, expressing the encoded portion of the SMP protein or peptide (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the SMP protein or peptide.

The invention further encompasses nucleic acid molecules that differ from one of the nucleotide sequences shown in Appendix A (and portions thereof) due to degeneracy of the genetic code and thus encode the same SMP protein as that encoded by the nucleotide sequences shown in Appendix A. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in Appendix B. In a still further embodiment, the nucleic acid molecule of the invention encodes a full length *C. glutamicum* protein which is substantially homologous to an amino acid sequence of Appendix B (encoded by an open reading frame shown in Appendix A).

It will be understood by one of ordinary skill in the art that in one embodiment the sequences of the invention are not meant to include the sequences of the prior art, such as those Genbank sequences set forth in Tables 2 or 4 which were available prior to the present invention. In one embodiment, the invention includes nucleotide and amino acid sequences having a percent identity to a nucleotide or amino acid sequence of the invention which is greater than that of a sequence of the prior art (*e.g.*, a Genbank sequence (or the protein encoded by such a sequence) set forth in Tables 2 or 4). For example, the invention includes a nucleotide sequence which is greater than and/or at least 58% identical to the nucleotide sequence designated RXA00014 (SEQ ID NO:41), a nucleotide sequence which is greater than and/or at least % identical to the nucleotide sequence designated RXA00195 (SEQ ID NO:399), and a nucleotide sequence which is greater than and/or at least 42% identical to the nucleotide sequence designated RXA00196 (SEQ ID NO:401). One of ordinary skill in the art would be able to calculate the lower threshold of percent identity for any given sequence of the invention by examining the GAP-calculated percent identity scores set forth in Table 4 for each of the three top hits for the given sequence, and by subtracting the highest GAP-calculated percent identity from 100 percent. One of ordinary skill in the art will also appreciate that nucleic acid and amino acid sequences having percent identities greater than the

lower threshold so calculated (*e.g.*, at least 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more identical) are also encompassed by the invention.

In addition to the *C. glutamicum* SMP nucleotide sequences shown in Appendix A, it will be appreciated by those of ordinary skill in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of SMP proteins may exist within a population (*e.g.*, the *C. glutamicum* population). Such genetic polymorphism in the SMP gene may exist among individuals within a population due to natural variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding an SMP protein, preferably a *C. glutamicum* SMP protein. Such natural variations can typically result in 1-5% variance in the nucleotide sequence of the SMP gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in SMP that are the result of natural variation and that do not alter the functional activity of SMP proteins are intended to be within the scope of the invention.

Nucleic acid molecules corresponding to natural variants and non-*C. glutamicum* homologues of the *C. glutamicum* SMP DNA of the invention can be isolated based on their homology to the *C. glutamicum* SMP nucleic acid disclosed herein using the *C. glutamicum* DNA, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions. Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising a nucleotide sequence of Appendix A. In other embodiments, the nucleic acid is at least 30, 50, 100, 250 or more nucleotides in length. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 65%, more preferably at least about 70%, and even more preferably at least about 75% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those of ordinary skill in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C.

Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to a sequence of Appendix A corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein). In one embodiment, the nucleic acid encodes a natural *C. glutamicum* SMP protein.

In addition to naturally-occurring variants of the SMP sequence that may exist in the population, one of ordinary skill in the art will further appreciate that changes can be introduced by mutation into a nucleotide sequence of Appendix A, thereby leading to changes in the amino acid sequence of the encoded SMP protein, without altering the functional ability of the SMP protein. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in a sequence of Appendix A. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of one of the SMP proteins (Appendix B) without altering the activity of said SMP protein, whereas an "essential" amino acid residue is required for SMP protein activity. Other amino acid residues, however, (*e.g.*, those that are not conserved or only semi-conserved in the domain having SMP activity) may not be essential for activity and thus are likely to be amenable to alteration without altering SMP activity.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding SMP proteins that contain changes in amino acid residues that are not essential for SMP activity. Such SMP proteins differ in amino acid sequence from a sequence contained in Appendix B yet retain at least one of the SMP activities described herein. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 50% homologous to an amino acid sequence of Appendix B and is capable of participate in the metabolism of carbon compounds such as sugars, or in the biosynthesis of high-energy compounds in *C. glutamicum*, or has one or more activities set forth in Table 1. Preferably, the protein encoded by the nucleic acid molecule is at least about 50-60% homologous to one of the sequences in Appendix B, more preferably at least about 60-70% homologous to one of the sequences in Appendix B, even more preferably at least about 70-80%, 80-90%, 90-95% homologous to one of the sequences in Appendix B, and most preferably at least about 96%, 97%, 98%, or 99% homologous to one of the sequences in Appendix B.

To determine the percent homology of two amino acid sequences (*e.g.*, one of the sequences of Appendix B and a mutant form thereof) or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in

the sequence of one protein or nucleic acid for optimal alignment with the other protein or nucleic acid). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in one sequence (*e.g.*, one of the sequences of Appendix B) is occupied by the same amino acid residue or nucleotide as the corresponding position in the other sequence (*e.g.*, a mutant form of the sequence selected from Appendix B), then the molecules are homologous at that position (*i.e.*, as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity"). The percent homology between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 100).

An isolated nucleic acid molecule encoding an SMP protein homologous to a protein sequence of Appendix B can be created by introducing one or more nucleotide substitutions, additions or deletions into a nucleotide sequence of Appendix A such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced into one of the sequences of Appendix A by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an SMP protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an SMP coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for an SMP activity described herein to identify mutants that retain SMP activity. Following mutagenesis of one of the sequences of Appendix A, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using, for example, assays described herein (see Example 8 of the Exemplification).

In addition to the nucleic acid molecules encoding SMP proteins described above, another aspect of the invention pertains to isolated nucleic acid molecules which

are antisense thereto. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded DNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire SMP coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding an SMP protein. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues (*e.g.*, the entire coding region of NO. 3 (RXA01626) comprises nucleotides 1 to 345). In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding SMP. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding SMP disclosed herein (*e.g.*, the sequences set forth in Appendix A), antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of SMP mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of SMP mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of SMP mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-

methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a cell or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an SMP protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. The antisense molecule can be modified such that it specifically binds to a receptor or an antigen expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecule to a peptide or an antibody which binds to a cell surface receptor or antigen. The antisense nucleic acid molecule can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong prokaryotic, viral, or eukaryotic promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids. Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave SMP mRNA transcripts to thereby inhibit translation of SMP

mRNA. A ribozyme having specificity for an SMP-encoding nucleic acid can be designed based upon the nucleotide sequence of an SMP cDNA disclosed herein (*i.e.*, SEQ ID NO. 3 (RXA01626) in Appendix A). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an SMP-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071 and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, SMP mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.

Alternatively, SMP gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of an SMP nucleotide sequence (*e.g.*, an SMP promoter and/or enhancers) to form triple helical structures that prevent transcription of an SMP gene in target cells. See generally, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15.

B. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an SMP protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells. Preferred regulatory sequences are, for example, promoters such as cos-, tac-, trp-, tet-, trp-tet-, lpp-, lac-, lpp-lac-, $lacI^q$-, T7-, T5-, T3-, gal-, trc-, ara-, SP6-, arny, SPO2, λ-P_R- or λ P_L, which are used preferably in bacteria. Additional regulatory sequences are, for example, promoters from yeasts and fungi, such as ADC1, MFα, AC, P-60, CYC1, GAPDH, TEF, rp28, ADH, promoters from plants such as CaMV/35S, SSU, OCS, lib4, usp, STLS1, B33, nos or ubiquitin- or phaseolin-promoters. It is also possible to use artificial promoters. It will be appreciated by those of ordinary skill in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, SMP proteins, mutant forms of SMP proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of SMP proteins in prokaryotic or eukaryotic cells. For example, SMP genes can be expressed in bacterial cells such as *C. glutamicum*, insect cells (using baculovirus expression vectors), yeast and other fungal cells (see Romanos, M.A. *et al.* (1992) "Foreign gene expression in yeast: a review", *Yeast* 8: 423-488; van den Hondel, C.A.M.J.J. *et al.* (1991) "Heterologous gene expression in filamentous fungi" in: More Gene Manipulations in Fungi, J.W. Bennet & L.L. Lasure, eds., p. 396-428: Academic Press: San Diego; and van den Hondel, C.A.M.J.J. & Punt, P.J. (1991) "Gene transfer systems and vector development for filamentous fungi, in: Applied Molecular Genetics of Fungi, Peberdy, J.F. *et al.*, eds., p. 1-28, Cambridge University Press: Cambridge),

algae and multicellular plant cells (see Schmidt, R. and Willmitzer, L. (1988) High efficiency *Agrobacterium tumefaciens* –mediated transformation of *Arabidopsis thaliana* leaf and cotyledon explants" *Plant Cell Rep*: 583-586), or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein but also to the C-terminus or fused within suitable regions in the proteins. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase.

Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. In one embodiment, the coding sequence of the SMP protein is cloned into a pGEX expression vector to create a vector encoding a fusion protein comprising, from the N-terminus to the C-terminus, GST-thrombin cleavage site-X protein. The fusion protein can be purified by affinity chromatography using glutathione-agarose resin. Recombinant SMP protein unfused to GST can be recovered by cleavage of the fusion protein with thrombin.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, (1988) *Gene* 69:301-315), pLG338, pACYC184, pBR322, pUC18, pUC19, pKC30, pRep4, pHS1, pHS2, pPLc236, pMBL24, pLG200, pUR290, pIN-III113-B1, λgt11, pBdCl, and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89; and Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York IBSN 0 444 904018). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the

pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident λ prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter. For transformation of other varieties of bacteria, appropriate vectors may be selected. For example, the plasmids pIJ101, pIJ364, pIJ702 and pIJ361 are known to be useful in transforming Streptomyces, while plasmids pUB110, pC194, or pBD214 are suited for transformation of Bacillus species. Several plasmids of use in the transfer of genetic information into Corynebacterium include pHM1519, pBL1, pSA77, or pAJ667 (Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York IBSN 0 444 904018).

One strategy to maximize recombinant protein expression is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in the bacterium chosen for expression, such as *C. glutamicum* (Wada *et al.* (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the SMP protein expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari, *et al.*, (1987) *Embo J.* 6:229-234), 2 μ, pAG-1, Yep6, Yep13, pEMBLYe23, pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz *et al.*, (1987) *Gene* 54:113-123), and pYES2 (Invitrogen Corporation, San Diego, CA). Vectors and methods for the construction of vectors appropriate for use in other fungi, such as the filamentous fungi, include those detailed in: van den Hondel, C.A.M.J.J. & Punt, P.J. (1991) "Gene transfer systems and vector development for filamentous fungi, in: Applied Molecular Genetics of Fungi, J.F. Peberdy, *et al.*, eds., p. 1-28, Cambridge University Press: Cambridge, and Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York (IBSN 0 444 904018).

Alternatively, the SMP proteins of the invention can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.* (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

In another embodiment, the SMP proteins of the invention may be expressed in unicellular plant cells (such as algae) or in plant cells from higher plants (*e.g.*, the

spermatophytes, such as crop plants). Examples of plant expression vectors include those detailed in: Becker, D., Kemper, E., Schell, J. and Masterson, R. (1992) "New plant binary vectors with selectable markers located proximal to the left border", *Plant Mol. Biol.* 20: 1195-1197; and Bevan, M.W. (1984) "Binary *Agrobacterium* vectors for plant transformation", *Nucl. Acid. Res.* 12: 8711-8721, and include pLGV23, pGHlac+, pBIN19, pAK2004, and pDH51 (Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York IBSN 0 444 904018). .

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.* (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.* (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle (1989) *PNAS* 86:5473-5477), pancreas-specific promoters (Edlund *et al.* (1985) *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the α-fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in

a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to SMP mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, an SMP protein can be expressed in bacterial cells such as *C. glutamicum*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to one of ordinary skill in the art. Microorganisms related to *Corynebacterium glutamicum* which may be conveniently used as host cells for the nucleic acid and protein molecules of the invention are set forth in Table 3.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection", "conjugation" and "transduction" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, linear DNA or RNA (*e.g.*, a linearized vector or a gene construct alone without a vector) or nucleic acid in the form of a vector (*e.g.*, a plasmid, phage, phasmid, phagemid, transposon or other DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, natural competence, chemical-mediated transfer, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*Molecular*

Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding an SMP protein or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by, for example, drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

To create a homologous recombinant microorganism, a vector is prepared which contains at least a portion of an SMP gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the SMP gene. Preferably, this SMP gene is a *Corynebacterium glutamicum* SMP gene, but it can be a homologue from a related bacterium or even from a mammalian, yeast, or insect source. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous SMP gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous SMP gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous SMP protein). In the homologous recombination vector, the altered portion of the SMP gene is flanked at its 5' and 3' ends by additional nucleic acid of the SMP gene to allow for homologous recombination to occur between the exogenous SMP gene carried by the vector and an endogenous SMP gene in a microorganism. The additional flanking SMP nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see *e.g.*, Thomas, K.R., and Capecchi, M.R. (1987) Cell 51: 503 for a description of homologous recombination vectors). The vector is introduced into a microorganism (*e.g.*, by electroporation) and cells in which the introduced SMP gene has homologously recombined with the endogenous SMP gene are selected, using art-known techniques.

In another embodiment, recombinant microorganisms can be produced which contain selected systems which allow for regulated expression of the introduced gene.

For example, inclusion of an SMP gene on a vector placing it under control of the lac operon permits expression of the SMP gene only in the presence of IPTG. Such regulatory systems are well known in the art.

In another embodiment, an endogenous SMP gene in a host cell is disrupted (*e.g.*, by homologous recombination or other genetic means known in the art) such that expression of its protein product does not occur. In another embodiment, an endogenous or introduced SMP gene in a host cell has been altered by one or more point mutations, deletions, or inversions, but still encodes a functional SMP protein. In still another embodiment, one or more of the regulatory regions (*e.g.*, a promoter, repressor, or inducer) of an SMP gene in a microorganism has been altered (*e.g.*, by deletion, truncation, inversion, or point mutation) such that the expression of the SMP gene is modulated. One of ordinary skill in the art will appreciate that host cells containing more than one of the described SMP gene and protein modifications may be readily produced using the methods of the invention, and are meant to be included in the present invention.

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) an SMP protein. Accordingly, the invention further provides methods for producing SMP proteins using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding an SMP protein has been introduced, or into which genome has been introduced a gene encoding a wild-type or altered SMP protein) in a suitable medium until SMP protein is produced. In another embodiment, the method further comprises isolating SMP proteins from the medium or the host cell.

C. Isolated SMP Proteins

Another aspect of the invention pertains to isolated SMP proteins, and biologically active portions thereof. An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of SMP protein in which the protein is separated from cellular components of the cells in which it is naturally or recombinantly produced. In one embodiment, the language "substantially free of cellular material" includes preparations of SMP protein having less than about 30% (by dry weight) of non-SMP protein (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-SMP protein, still more preferably less than about 10% of non-SMP protein, and most preferably less

than about 5% non-SMP protein. When the SMP protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the protein preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of SMP protein in which the protein is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of SMP protein having less than about 30% (by dry weight) of chemical precursors or non-SMP chemicals, more preferably less than about 20% chemical precursors or non-SMP chemicals, still more preferably less than about 10% chemical precursors or non-SMP chemicals, and most preferably less than about 5% chemical precursors or non-SMP chemicals. In preferred embodiments, isolated proteins or biologically active portions thereof lack contaminating proteins from the same organism from which the SMP protein is derived. Typically, such proteins are produced by recombinant expression of, for example, a *C. glutamicum* SMP protein in a microorganism such as *C. glutamicum.*

An isolated SMP protein or a portion thereof of the invention can participate in the metabolism of carbon compounds such as sugars, or in the production of energy compounds (*e.g.*, by oxidative phosphorylation) utilized to drive unfavorable metabolic pathways, or has one or more of the activities set forth in Table 1. In preferred embodiments, the protein or portion thereof comprises an amino acid sequence which is sufficiently homologous to an amino acid sequence of Appendix B such that the protein or portion thereof maintains the ability to perform a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*. The portion of the protein is preferably a biologically active portion as described herein. In another preferred embodiment, an SMP protein of the invention has an amino acid sequence shown in Appendix B. In yet another preferred embodiment, the SMP protein has an amino acid sequence which is encoded by a nucleotide sequence which hybridizes, *e.g.*, hybridizes under stringent conditions, to a nucleotide sequence of Appendix A. In still another preferred embodiment, the SMP protein has an amino acid sequence which is encoded by a nucleotide sequence that is at least about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more

preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to one of the nucleic acid sequences of Appendix A, or a portion thereof. Ranges and identity values intermediate to the above-recited values, (*e.g.*, 70-90% identical or 80-95% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included. The preferred SMP proteins of the present invention also preferably possess at least one of the SMP activities described herein. For example, a preferred SMP protein of the present invention includes an amino acid sequence encoded by a nucleotide sequence which hybridizes, *e.g.*, hybridizes under stringent conditions, to a nucleotide sequence of Appendix A, and which can perform a function involved in the metabolism of carbon compounds such as sugars or in the generation of energy molecules (*e.g.*, ATP) by processes such as oxidative phosphorylation in *Corynebacterium glutamicum*, or which has one or more of the activities set forth in Table 1.

In other embodiments, the SMP protein is substantially homologous to an amino acid sequence of Appendix B and retains the functional activity of the protein of one of the sequences of Appendix B yet differs in amino acid sequence due to natural variation or mutagenesis, as described in detail in subsection I above. Accordingly, in another embodiment, the SMP protein is a protein which comprises an amino acid sequence which is at least about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to an entire amino acid sequence of Appendix B and which has at least one of the SMP activities described herein. Ranges and identity values intermediate to the above-recited values, (*e.g.*, 70-90% identical or 80-95% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included. In another embodiment, the invention pertains to a full length *C. glutamicum* protein which is substantially homologous to an entire amino acid sequence of Appendix B.

Biologically active portions of an SMP protein include peptides comprising amino acid sequences derived from the amino acid sequence of an SMP protein, *e.g.*, the an amino acid sequence shown in Appendix B or the amino acid sequence of a protein homologous to an SMP protein, which include fewer amino acids than a full length SMP protein or the full length protein which is homologous to an SMP protein, and exhibit at

least one activity of an SMP protein. Typically, biologically active portions (peptides, *e.g.*, peptides which are, for example, 5, 10, 15, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100 or more amino acids in length) comprise a domain or motif with at least one activity of an SMP protein. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the activities described herein. Preferably, the biologically active portions of an SMP protein include one or more selected domains/motifs or portions thereof having biological activity.

SMP proteins are preferably produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the protein is cloned into an expression vector (as described above), the expression vector is introduced into a host cell (as described above) and the SMP protein is expressed in the host cell. The SMP protein can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques. Alternative to recombinant expression, an SMP protein, polypeptide, or peptide can be synthesized chemically using standard peptide synthesis techniques. Moreover, native SMP protein can be isolated from cells (*e.g.*, endothelial cells), for example using an anti-SMP antibody, which can be produced by standard techniques utilizing an SMP protein or fragment thereof of this invention.

The invention also provides SMP chimeric or fusion proteins. As used herein, an SMP "chimeric protein" or "fusion protein" comprises an SMP polypeptide operatively linked to a non-SMP polypeptide. An "SMP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to an SMP protein, whereas a "non-SMP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the SMP protein, *e.g.*, a protein which is different from the SMP protein and which is derived from the same or a different organism. Within the fusion protein, the term "operatively linked" is intended to indicate that the SMP polypeptide and the non-SMP polypeptide are fused in-frame to each other. The non-SMP polypeptide can be fused to the N-terminus or C-terminus of the SMP polypeptide. For example, in one embodiment the fusion protein is a GST-SMP fusion protein in which the SMP sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant SMP proteins. In another embodiment, the fusion protein is an SMP protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of an SMP protein can be increased through use of a heterologous signal sequence.

Preferably, an SMP chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the

different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds. John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). An SMP-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the SMP protein.

Homologues of the SMP protein can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation of the SMP protein. As used herein, the term "homologue" refers to a variant form of the SMP protein which acts as an agonist or antagonist of the activity of the SMP protein. An agonist of the SMP protein can retain substantially the same, or a subset, of the biological activities of the SMP protein. An antagonist of the SMP protein can inhibit one or more of the activities of the naturally occurring form of the SMP protein, by, for example, competitively binding to a downstream or upstream member of the sugar molecule metabolic cascade or the energy-producing pathway which includes the SMP protein.

In an alternative embodiment, homologues of the SMP protein can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the SMP protein for SMP protein agonist or antagonist activity. In one embodiment, a variegated library of SMP variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of SMP variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential SMP sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of SMP sequences therein. There are a variety of methods which can be used to produce libraries of potential SMP homologues from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding

the desired set of potential SMP sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477.

In addition, libraries of fragments of the SMP protein coding can be used to generate a variegated population of SMP fragments for screening and subsequent selection of homologues of an SMP protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an SMP coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the SMP protein.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of SMP homologues. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify SMP homologues (Arkin and Yourvan (1992) *PNAS* *89*:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

In another embodiment, cell based assays can be exploited to analyze a variegated SMP library, using methods well known in the art.

D. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, fusion proteins, primers, vectors, and host cells described herein can be used in one or more of the following methods: identification of *C. glutamicum* and related organisms; mapping of genomes of organisms related to *C. glutamicum*; identification and localization of *C. glutamicum* sequences of interest; evolutionary studies; determination of SMP protein

regions required for function; modulation of an SMP protein activity; modulation of the metabolism of one or more sugars; modulation of high-energy molecule production in a cell (*i.e.*, ATP, NADPH); and modulation of cellular production of a desired compound, such as a fine chemical.

The SMP nucleic acid molecules of the invention have a variety of uses. First, they may be used to identify an organism as being *Corynebacterium glutamicum* or a close relative thereof. Also, they may be used to identify the presence of *C. glutamicum* or a relative thereof in a mixed population of microorganisms. The invention provides the nucleic acid sequences of a number of *C. glutamicum* genes; by probing the extracted genomic DNA of a culture of a unique or mixed population of microorganisms under stringent conditions with a probe spanning a region of a *C. glutamicum* gene which is unique to this organism, one can ascertain whether this organism is present. Although *Corynebacterium glutamicum* itself is nonpathogenic, it is related to pathogenic species, such as *Corynebacterium diphtheriae*. *Corynebacterium diphtheriae* is the causative agent of diphtheria, a rapidly developing, acute, febrile infection which involves both local and systemic pathology. In this disease, a local lesion develops in the upper respiratory tract and involves necrotic injury to epithelial cells; the bacilli secrete toxin which is disseminated through this lesion to distal susceptible tissues of the body. Degenerative changes brought about by the inhibition of protein synthesis in these tissues, which include heart, muscle, peripheral nerves, adrenals, kidneys, liver and spleen, result in the systemic pathology of the disease. Diphtheria continues to have high incidence in many parts of the world, including Africa, Asia, Eastern Europe and the independent states of the former Soviet Union. An ongoing epidemic of diphtheria in the latter two regions has resulted in at least 5,000 deaths since 1990.

In one embodiment, the invention provides a method of identifying the presence or activity of *Cornyebacterium diphtheriae* in a subject. This method includes detection of one or more of the nucleic acid or amino acid sequences of the invention (*e.g.*, the sequences set forth in Appendix A or Appendix B) in a subject, thereby detecting the presence or activity of *Corynebacterium diphtheriae* in the subject. *C. glutamicum* and *C. diphtheriae* are related bacteria, and many of the nucleic acid and protein molecules in C. *glutamicum* are homologous to *C. diphtheriae* nucleic acid and protein molecules, and can therefore be used to detect *C. diphtheriae* in a subject.

The nucleic acid and protein molecules of the invention may also serve as markers for specific regions of the genome. This has utility not only in the mapping of the genome, but also for functional studies of *C. glutamicum* proteins. For example, to identify the region of the genome to which a particular *C. glutamicum* DNA-binding protein binds, the *C. glutamicum* genome could be digested, and the fragments incubated

with the DNA-binding protein. Those which bind the protein may be additionally probed with the nucleic acid molecules of the invention, preferably with readily detectable labels; binding of such a nucleic acid molecule to the genome fragment enables the localization of the fragment to the genome map of *C. glutamicum*, and, when performed multiple times with different enzymes, facilitates a rapid determination of the nucleic acid sequence to which the protein binds. Further, the nucleic acid molecules of the invention may be sufficiently homologous to the sequences of related species such that these nucleic acid molecules may serve as markers for the construction of a genomic map in related bacteria, such as *Brevibacterium lactofermentum*.

The SMP nucleic acid molecules of the invention are also useful for evolutionary and protein structural studies. The metabolic and energy-releasing processes in which the molecules of the invention participate are utilized by a wide variety of prokaryotic and eukaryotic cells; by comparing the sequences of the nucleic acid molecules of the present invention to those encoding similar enzymes from other organisms, the evolutionary relatedness of the organisms can be assessed. Similarly, such a comparison permits an assessment of which regions of the sequence are conserved and which are not, which may aid in determining those regions of the protein which are essential for the functioning of the enzyme. This type of determination is of value for protein engineering studies and may give an indication of what the protein can tolerate in terms of mutagenesis without losing function.

Manipulation of the SMP nucleic acid molecules of the invention may result in the production of SMP proteins having functional differences from the wild-type SMP proteins. These proteins may be improved in efficiency or activity, may be present in greater numbers in the cell than is usual, or may be decreased in efficiency or activity.

The invention provides methods for screening molecules which modulate the activity of an SMP protein, either by interacting with the protein itself or a substrate or binding partner of the SMP protein, or by modulating the transcription or translation of an SMP nucleic acid molecule of the invention. In such methods, a microorganism expressing one or more SMP proteins of the invention is contacted with one or more test compounds, and the effect of each test compound on the activity or level of expression of the SMP protein is assessed.

There are a number of mechanisms by which the alteration of an SMP protein of the invention may directly affect the yield, production, and/or efficiency of production of a fine chemical from a *C. glutamicum* strain incorporating such an altered protein. The degradation of high-energy carbon molecules such as sugars, and the conversion of compounds such as NADH and $FADH_2$ to more useful forms via oxidative phosphorylation results in a number of compounds which themselves may be desirable

fine chemicals, such as pyruvate, ATP, NADH, and a number of intermediate sugar compounds. Further, the energy molecules (such as ATP) and the reducing equivalents (such as NADH or NADPH) produced by these metabolic pathways are utilized in the cell to drive reactions which would otherwise be energetically unfavorable. Such unfavorable reactions include many biosynthetic pathways for fine chemicals. By improving the ability of the cell to utilize a particular sugar (*e.g.*, by manipulating the genes encoding enzymes involved in the degradation and conversion of that sugar into energy for the cell), one may increase the amount of energy available to permit unfavorable, yet desired metabolic reactions (*e.g.*, the biosynthesis of a desired fine chemical) to occur.

Further, modulation of one or more pathways involved in sugar utilization permits optimization of the conversion of the energy contained within the sugar molecule to the production of one or more desired fine chemicals. For example, by reducing the activity of enzymes involved in, for example, gluconeogenesis, more ATP is available to drive desired biochemical reactions (such as fine chemical biosyntheses) in the cell. Also, the overall production of energy molecules from sugars may be modulated to ensure that the cell maximizes its energy production from each sugar molecule. Inefficient sugar utilization can lead to excess CO_2 production and excess energy, which may result in futile metabolic cycles. By improving the metabolism of sugar molecules, the cell should be able to function more efficiently, with a need for fewer carbon molecules. This should result in an improved fine chemical product: sugar molecule ratio (improved carbon yield), and permits a decrease in the amount of sugars that must be added to the medium in large-scale fermentor culture of such engineered *C. glutamicum*.

The mutagenesis of one or more SMP genes of the invention may also result in SMP proteins having altered activities which indirectly impact the production of one or more desired fine chemicals from *C. glutamicum*. For example, by increasing the efficiency of utilization of one or more sugars (such that the conversion of the sugar to useful energy molecules is improved), or by increasing the efficiency of conversion of reducing equivalents to useful energy molecules (*e.g.*, by improving the efficiency of oxidative phosphorylation, or the activity of the ATP synthase), one can increase the amount of these high-energy compounds available to the cell to drive normally unfavorable metabolic processes. These processes include the construction of cell walls, transcription, translation, and the biosynthesis of compounds necessary for growth and division of the cells (*e.g.*, nucleotides, amino acids, vitamins, lipids, etc.) (Lengeler *et al.* (1999) Biology of Prokaryotes, Thieme Verlag: Stuttgart, p. 88-109; 913-918; 875-899). By improving the growth and multiplication of these engineered cells, it is possible to

increase both the viability of the cells in large-scale culture, and also to improve their rate of division, such that a relatively larger number of cells can survive in fermentor culture. The yield, production, or efficiency of production may be increased, at least due to the presence of a greater number of viable cells, each producing the desired fine chemical.

Further, many of the degradation products produced during sugar metabolism are themselves utilized by the cell as precursors or intermediates for the production of a number of other useful compounds, some of which are fine chemicals. For example, pyruvate is converted into the amino acid alanine, and ribose-5-phosphate is an integral part of, for example, nucleotide molecules. The amount and efficiency of sugar metabolism, then, has a profound effect on the availability of these degradation products in the cell. By increasing the ability of the cell to process sugars, either in terms of efficiency of existing pathways (*e.g.*, by engineering enzymes involved in these pathways such that they are optimized in activity), or by increasing the availability of the enzymes involved in such pathways (*e.g.*, by increasing the number of these enzymes present in the cell), it is possible to also increase the availability of these degradation products in the cell, which should in turn increase the production of many different other desirable compounds in the cell (*e.g.*, fine chemicals).

The aforementioned mutagenesis strategies for SMP proteins to result in increased yields of a fine chemical from *C. glutamicum* are not meant to be limiting; variations on these strategies will be readily apparent to one of ordinary skill in the art. Using such strategies, and incorporating the mechanisms disclosed herein, the nucleic acid and protein molecules of the invention may be utilized to generate *C. glutamicum* or related strains of bacteria expressing mutated SMP nucleic acid and protein molecules such that the yield, production, and/or efficiency of production of a desired compound is improved. This desired compound may be any product produced by *C. glutamicum*, which includes the final products of biosynthesis pathways and intermediates of naturally-occurring metabolic pathways, as well as molecules which do not naturally occur in the metabolism of *C. glutamicum*, but which are produced by a *C. glutamicum* strain of the invention.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patent applications, patents, published patent applications, Tables, Appendices, and the sequence listing cited throughout this application are hereby incorporated by reference.

Exemplification

Example 1: Preparation of total genomic DNA of *Corynebacterium glutamicum* ATCC 13032

A culture of *Corynebacterium glutamicum* (ATCC 13032) was grown overnight at 30°C with vigorous shaking in BHI medium (Difco). The cells were harvested by centrifugation, the supernatant was discarded and the cells were resuspended in 5 ml buffer-I (5% of the original volume of the culture — all indicated volumes have been calculated for 100 ml of culture volume). Composition of buffer-I: 140.34 g/l sucrose, 2.46 g/l $MgSO_4 \times 7H_2O$, 10 ml/l KH_2PO_4 solution (100 g/l, adjusted to pH 6.7 with KOH), 50 ml/l M12 concentrate (10 g/l $(NH_4)_2SO_4$, 1 g/l NaCl, 2 g/l $MgSO_4 \times 7H_2O$, 0.2 g/l $CaCl_2$, 0.5 g/l yeast extract (Difco), 10 ml/l trace-elements-mix (200 mg/l $FeSO_4 \times H_2O$, 10 mg/l $ZnSO_4 \times 7\ H_2O$, 3 mg/l $MnCl_2 \times 4\ H_2O$, 30 mg/l H_3BO_3 20 mg/l $CoCl_2 \times 6\ H_2O$, 1 mg/l $NiCl_2 \times 6\ H_2O$, 3 mg/l $Na_2MoO_4 \times 2\ H_2O$, 500 mg/l complexing agent (EDTA or critic acid), 100 ml/l vitamins-mix (0.2 mg/l biotin, 0.2 mg/l folic acid, 20 mg/l p-amino benzoic acid, 20 mg/l riboflavin, 40 mg/l ca-panthothenate, 140 mg/l nicotinic acid, 40 mg/l pyridoxole hydrochloride, 200 mg/l myo-inositol). Lysozyme was added to the suspension to a final concentration of 2.5 mg/ml. After an approximately 4 h incubation at 37°C, the cell wall was degraded and the resulting protoplasts are harvested by centrifugation. The pellet was washed once with 5 ml buffer-I and once with 5 ml TE-buffer (10 mM Tris-HCl, 1 mM EDTA, pH 8). The pellet was resuspended in 4 ml TE-buffer and 0.5 ml SDS solution (10%) and 0.5 ml NaCl solution (5 M) are added. After adding of proteinase K to a final concentration of 200 µg/ml, the suspension is incubated for ca.18 h at 37°C. The DNA was purified by extraction with phenol, phenol-chloroform-isoamylalcohol and chloroform-isoamylalcohol using standard procedures. Then, the DNA was precipitated by adding 1/50 volume of 3 M sodium acetate and 2 volumes of ethanol, followed by a 30 min incubation at -20°C and a 30 min centrifugation at 12,000 rpm in a high speed centrifuge using a SS34 rotor (Sorvall). The DNA was dissolved in 1 ml TE-buffer containing 20 µg/ml RNaseA and dialysed at 4°C against 1000 ml TE-buffer for at least 3 hours. During this time, the buffer was exchanged 3 times. To aliquots of 0.4 ml of the dialysed DNA solution, 0.4 ml of 2 M LiCl and 0.8 ml of ethanol are added. After a 30

min incubation at -20°C, the DNA was collected by centrifugation (13,000 rpm, Biofuge Fresco, Heraeus, Hanau, Germany). The DNA pellet was dissolved in TE-buffer. DNA prepared by this procedure could be used for all purposes, including southern blotting or construction of genomic libraries.

Example 2: Construction of genomic libraries in *Escherichia coli* of *Corynebacterium glutamicum* ATCC13032.

Using DNA prepared as described in Example 1, cosmid and plasmid libraries were constructed according to known and well established methods (*see e.g.,* Sambrook, J. *et al.* (1989) "Molecular Cloning : A Laboratory Manual", Cold Spring Harbor Laboratory Press, or Ausubel, F.M. *et al.* (1994) "Current Protocols in Molecular Biology", John Wiley & Sons.)

Any plasmid or cosmid could be used. Of particular use were the plasmids pBR322 (Sutcliffe, J.G. (1979) *Proc. Natl. Acad. Sci. USA*, 75:3737-3741); pACYC177 (Change & Cohen (1978) *J. Bacteriol* 134:1141-1156), plasmids of the pBS series (pBSSK+, pBSSK- and others; Stratagene, LaJolla, USA), or cosmids as SuperCos1 (Stratagene, LaJolla, USA) or Lorist6 (Gibson, T.J., Rosenthal A. and Waterson, R.H. (1987) *Gene* 53:283-286. Gene libraries specifically for use in *C. glutamicum* may be constructed using plasmid pSL109 (Lee, H.-S. and A. J. Sinskey (1994) *J. Microbiol. Biotechnol.* 4: 256-263).

Example 3: DNA Sequencing and Computational Functional Analysis

Genomic libraries as described in Example 2 were used for DNA sequencing according to standard methods, in particular by the chain termination method using ABI377 sequencing machines (see *e.g.*, Fleischman, R.D. *et al.* (1995) "Whole-genome Random Sequencing and Assembly of Haemophilus Influenzae Rd., *Science*, 269:496-512). Sequencing primers with the following nucleotide sequences were used: 5'-GGAAACAGTATGACCATG-3' or 5'-GTAAAACGACGGCCAGT-3'.

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Example 4: *In vivo* Mutagenesis

In vivo mutagenesis of *Corynebacterium glutamicum* can be performed by passage of plasmid (or other vector) DNA through *E. coli* or other microorganisms (*e.g. Bacillus* spp. or yeasts such as *Saccharomyces cerevisiae*) which are impaired in their capabilities to maintain the integrity of their genetic information. Typical mutator strains have mutations in the genes for the DNA repair system (*e.g.*, mutHLS, mutD, mutT, etc.; for reference, see Rupp, W.D. (1996) DNA repair mechanisms, in: *Escherichia coli* and *Salmonella*, p. 2277-2294, ASM: Washington.) Such strains are well known to those of ordinary skill in the art. The use of such strains is illustrated, for example, in Greener, A. and Callahan, M. (1994) *Strategies* 7: 32-34.

Example 5: DNA Transfer Between *Escherichia coli* and *Corynebacterium glutamicum*

Several *Corynebacterium* and *Brevibacterium* species contain endogenous plasmids (as *e.g.*, pHM1519 or pBL1) which replicate autonomously (for review see, *e.g.*, Martin, J.F. *et al.* (1987) *Biotechnology*, 5:137-146). Shuttle vectors for *Escherichia coli* and *Corynebacterium glutamicum* can be readily constructed by using standard vectors for *E. coli* (Sambrook, J. *et al.* (1989), "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Laboratory Press or Ausubel, F.M. *et al.* (1994) "Current Protocols in Molecular Biology", John Wiley & Sons) to which a origin or replication for and a suitable marker from *Corynebacterium glutamicum* is added. Such origins of replication are preferably taken from endogenous plasmids isolated from *Corynebacterium* and *Brevibacterium* species. Of particular use as transformation markers for these species are genes for kanamycin resistance (such as those derived from the Tn5 or Tn903 transposons) or chloramphenicol (Winnacker, E.L. (1987) "From Genes to Clones — Introduction to Gene Technology, VCH, Weinheim). There are numerous examples in the literature of the construction of a wide variety of shuttle vectors which replicate in both *E. coli and C. glutamicum*, and which can be used for several purposes, including gene over-expression (for reference, see *e.g.*, Yoshihama, M. *et al.* (1985) *J. Bacteriol.* 162:591-597, Martin J.F. *et al.* (1987) *Biotechnology*, 5:137-146 and Eikmanns, B.J. *et al.* (1991) *Gene*, 102:93-98).

Using standard methods, it is possible to clone a gene of interest into one of the shuttle vectors described above and to introduce such a hybrid vectors into strains of *Corynebacterium glutamicum*. Transformation of *C. glutamicum* can be achieved by protoplast transformation (Kastsumata, R. *et al.* (1984) *J. Bacteriol.* 159306-311), electroporation (Liebl, E. *et al.* (1989) *FEMS Microbiol. Letters*, 53:399-303) and in cases where special vectors are used, also by conjugation (as described *e.g.* in Schäfer, A *et al.* (1990) *J. Bacteriol.* 172:1663-1666). It is also possible to transfer the shuttle vectors for *C. glutamicum* to *E. coli* by preparing plasmid DNA from *C. glutamicum* (using standard methods well-known in the art) and transforming it into *E. coli*. This transformation step can be performed using standard methods, but it is advantageous to use an Mcr-deficient *E. coli* strain, such as NM522 (Gough & Murray (1983) *J. Mol. Biol.* 166:1-19).

Genes may be overexpressed in *C. glutamicum* strains using plasmids which comprise pCG1 (U.S. Patent No. 4,617,267) or fragments thereof, and optionally the gene for kanamycin resistance from TN903 (Grindley, N.D. and Joyce, C.M. (1980) *Proc. Natl. Acad. Sci. USA* 77(12): 7176-7180). In addition, genes may be

overexpressed in *C. glutamicum* strains using plasmid pSL109 (Lee, H.-S. and A. J. Sinskey (1994) *J. Microbiol. Biotechnol.* 4: 256-263).

Aside from the use of replicative plasmids, gene overexpression can also be achieved by integration into the genome. Genomic integration in *C. glutamicum* or other Corynebacterium or Brevibacterium species may be accomplished by well-known methods, such as homologous recombination with genomic region(s), restriction endonuclease mediated integration (REMI) (see, *e.g.*, DE Patent 19823834), or through the use of transposons. It is also possible to modulate the activity of a gene of interest by modifying the regulatory regions (*e.g.*, a promoter, a repressor, and/or an enhancer) by sequence modification, insertion, or deletion using site-directed methods (such as homologous recombination) or methods based on random events (such as transposon mutagenesis or REMI). Nucleic acid sequences which function as transcriptional terminators may also be inserted 3' to the coding region of one or more genes of the invention; such terminators are well-known in the art and are described, for example, in Winnacker, E.L. (1987) From Genes to Clones – Introduction to Gene Technology. VCH: Weinheim.

Example 6: Assessment of the Expression of the Mutant Protein

Observations of the activity of a mutated protein in a transformed host cell rely on the fact that the mutant protein is expressed in a similar fashion and in a similar quantity to that of the wild-type protein. A useful method to ascertain the level of transcription of the mutant gene (an indicator of the amount of mRNA available for translation to the gene product) is to perform a Northern blot (for reference see, for example, Ausubel *et al.* (1988) Current Protocols in Molecular Biology, Wiley: New York), in which a primer designed to bind to the gene of interest is labeled with a detectable tag (usually radioactive or chemiluminescent), such that when the total RNA of a culture of the organism is extracted, run on gel, transferred to a stable matrix and incubated with this probe, the binding and quantity of binding of the probe indicates the presence and also the quantity of mRNA for this gene. This information is evidence of the degree of transcription of the mutant gene. Total cellular RNA can be prepared from *Corynebacterium glutamicum* by several methods, all well-known in the art, such as that described in Bormann, E.R. *et al.* (1992) *Mol. Microbiol.* 6: 317-326.

To assess the presence or relative quantity of protein translated from this mRNA, standard techniques, such as a Western blot, may be employed (see, for example, Ausubel *et al.* (1988) Current Protocols in Molecular Biology, Wiley: New York). In this process, total cellular proteins are extracted, separated by gel electrophoresis, transferred to a matrix such as nitrocellulose, and incubated with a probe, such as an antibody, which

specifically binds to the desired protein. This probe is generally tagged with a chemiluminescent or colorimetric label which may be readily detected. The presence and quantity of label observed indicates the presence and quantity of the desired mutant protein present in the cell.

Example 7: Growth of Genetically Modified *Corynebacterium glutamicum* — Media and Culture Conditions

Genetically modified *Corynebacteria* are cultured in synthetic or natural growth media. A number of different growth media for Corynebacteria are both well-known and readily available (Lieb *et al.* (1989) *Appl. Microbiol. Biotechnol.*, 32:205-210; von der Osten *et al.* (1998) *Biotechnology Letters*, 11:11-16; Patent DE 4,120,867; Liebl (1992) "The Genus *Corynebacterium*, in: The Procaryotes, Volume II, Balows, A. *et al.*, eds. Springer-Verlag). These media consist of one or more carbon sources, nitrogen sources, inorganic salts, vitamins and trace elements. Preferred carbon sources are sugars, such as mono-, di-, or polysaccharides. For example, glucose, fructose, mannose, galactose, ribose, sorbose, ribulose, lactose, maltose, sucrose, raffinose, starch or cellulose serve as very good carbon sources. It is also possible to supply sugar to the media via complex compounds such as molasses or other by-products from sugar refinement. It can also be advantageous to supply mixtures of different carbon sources. Other possible carbon sources are alcohols and organic acids, such as methanol, ethanol, acetic acid or lactic acid. Nitrogen sources are usually organic or inorganic nitrogen compounds, or materials which contain these compounds. Exemplary nitrogen sources include ammonia gas or ammonia salts, such as NH_4Cl or $(NH_4)_2SO_4$, NH_4OH, nitrates, urea, amino acids or complex nitrogen sources like corn steep liquor, soy bean flour, soy bean protein, yeast extract, meat extract and others.

Inorganic salt compounds which may be included in the media include the chloride-, phosphorous- or sulfate- salts of calcium, magnesium, sodium, cobalt, molybdenum, potassium, manganese, zinc, copper and iron. Chelating compounds can be added to the medium to keep the metal ions in solution. Particularly useful chelating compounds include dihydroxyphenols, like catechol or protocatechuate, or organic acids, such as citric acid. It is typical for the media to also contain other growth factors, such as vitamins or growth promoters, examples of which include biotin, riboflavin, thiamin, folic acid, nicotinic acid, pantothenate and pyridoxin. Growth factors and salts frequently originate from complex media components such as yeast extract, molasses, corn steep liquor and others. The exact composition of the media compounds depends strongly on the immediate experiment and is individually decided for each specific case. Information about media optimization is available in the textbook "Applied Microbiol. Physiology, A

Practical Approach (*eds.* P.M. Rhodes, P.F. Stanbury, IRL Press (1997) pp. 53-73, ISBN 0 19 963577 3). It is also possible to select growth media from commercial suppliers, like standard 1 (Merck) or BHI (grain heart infusion, DIFCO) or others.

All medium components are sterilized, either by heat (20 minutes at 1.5 bar and 121°C) or by sterile filtration. The components can either be sterilized together or, if necessary, separately. All media components can be present at the beginning of growth, or they can optionally be added continuously or batchwise.

Culture conditions are defined separately for each experiment. The temperature should be in a range between 15°C and 45°C. The temperature can be kept constant or can be altered during the experiment. The pH of the medium should be in the range of 5 to 8.5, preferably around 7.0, and can be maintained by the addition of buffers to the media. An exemplary buffer for this purpose is a potassium phosphate buffer. Synthetic buffers such as MOPS, HEPES, ACES and others can alternatively or simultaneously be used. It is also possible to maintain a constant culture pH through the addition of NaOH or NH_4OH during growth. If complex medium components such as yeast extract are utilized, the necessity for additional buffers may be reduced, due to the fact that many complex compounds have high buffer capacities. If a fermentor is utilized for culturing the micro-organisms, the pH can also be controlled using gaseous ammonia.

The incubation time is usually in a range from several hours to several days. This time is selected in order to permit the maximal amount of product to accumulate in the broth. The disclosed growth experiments can be carried out in a variety of vessels, such as microtiter plates, glass tubes, glass flasks or glass or metal fermentors of different sizes. For screening a large number of clones, the microorganisms should be cultured in microtiter plates, glass tubes or shake flasks, either with or without baffles. Preferably 100 ml shake flasks are used, filled with 10% (by volume) of the required growth medium. The flasks should be shaken on a rotary shaker (amplitude 25 mm) using a speed-range of 100 – 300 rpm. Evaporation losses can be diminished by the maintenance of a humid atmosphere; alternatively, a mathematical correction for evaporation losses should be performed.

If genetically modified clones are tested, an unmodified control clone or a control clone containing the basic plasmid without any insert should also be tested. The medium is inoculated to an OD_{600} of O.5 – 1.5 using cells grown on agar plates, such as CM plates (10 g/l glucose, 2,5 g/l NaCl, 2 g/l urea, 10 g/l polypeptone, 5 g/l yeast extract, 5 g/l meat extract, 22 g/l NaCl, 2 g/l urea, 10 g/l polypeptone, 5 g/l yeast extract, 5 g/l meat extract, 22 g/l agar, pH 6.8 with 2M NaOH) that had been incubated at 30°C. Inoculation of the media is accomplished by either introduction of a saline suspension of *C. glutamicum* cells from CM plates or addition of a liquid preculture of this bacterium.

Example 8 – *In vitro* Analysis of the Function of Mutant Proteins

The determination of activities and kinetic parameters of enzymes is well established in the art. Experiments to determine the activity of any given altered enzyme must be tailored to the specific activity of the wild-type enzyme, which is well within the ability of one of ordinary skill in the art. Overviews about enzymes in general, as well as specific details concerning structure, kinetics, principles, methods, applications and examples for the determination of many enzyme activities may be found, for example, in the following references: Dixon, M., and Webb, E.C., (1979) Enzymes. Longmans: London; Fersht, (1985) Enzyme Structure and Mechanism. Freeman: New York; Walsh, (1979) Enzymatic Reaction Mechanisms. Freeman: San Francisco; Price, N.C., Stevens, L. (1982) Fundamentals of Enzymology. Oxford Univ. Press: Oxford; Boyer, P.D., ed. (1983) The Enzymes, 3rd ed. Academic Press: New York; Bisswanger, H., (1994) Enzymkinetik, 2nd ed. VCH: Weinheim (ISBN 3527300325); Bergmeyer, H.U., Bergmeyer, J., Graßl, M., eds. (1983-1986) Methods of Enzymatic Analysis, 3rd ed., vol. I-XII, Verlag Chemie: Weinheim; and Ullmann's Encyclopedia of Industrial Chemistry (1987) vol. A9, "Enzymes". VCH: Weinheim, p. 352-363.

The activity of proteins which bind to DNA can be measured by several well-established methods, such as DNA band-shift assays (also called gel retardation assays). The effect of such proteins on the expression of other molecules can be measured using reporter gene assays (such as that described in Kolmar, H. *et al.* (1995) *EMBO J.* 14: 3895-3904 and references cited therein). Reporter gene test systems are well known and established for applications in both pro- and eukaryotic cells, using enzymes such as beta-galactosidase, green fluorescent protein, and several others.

The determination of activity of membrane-transport proteins can be performed according to techniques such as those described in Gennis, R.B. (1989) "Pores, Channels and Transporters", in Biomembranes, Molecular Structure and Function, Springer: Heidelberg, p. 85-137; 199-234; and 270-322.

Example 9: Analysis of Impact of Mutant Protein on the Production of the Desired Product

The effect of the genetic modification in *C. glutamicum* on production of a desired compound (such as an amino acid) can be assessed by growing the modified microorganism under suitable conditions (such as those described above) and analyzing the medium and/or the cellular component for increased production of the desired product (*i.e.*, an amino acid). Such analysis techniques are well known to one of ordinary skill in the art, and include spectroscopy, thin layer chromatography, staining

methods of various kinds, enzymatic and microbiological methods, and analytical chromatography such as high performance liquid chromatography (see, for example, Ullman, Encyclopedia of Industrial Chemistry, vol. A2, p. 89-90 and p. 443-613, VCH: Weinheim (1985); Fallon, A. *et al.*, (1987) "Applications of HPLC in Biochemistry" in: Laboratory Techniques in Biochemistry and Molecular Biology, vol. 17; Rehm *et al.* (1993) Biotechnology, vol. 3, Chapter III: "Product recovery and purification", page 469-714, VCH: Weinheim; Belter, P.A. *et al.* (1988) Bioseparations: downstream processing for biotechnology, John Wiley and Sons; Kennedy, J.F. and Cabral, J.M.S. (1992) Recovery processes for biological materials, John Wiley and Sons; Shaeiwitz, J.A. and Henry, J.D. (1988) Biochemical separations, in: Ulmann's Encyclopedia of Industrial Chemistry, vol. B3, Chapter 11, page 1-27, VCH: Weinheim; and Dechow, F.J. (1989) Separation and purification techniques in biotechnology, Noyes Publications.)

In addition to the measurement of the final product of fermentation, it is also possible to analyze other components of the metabolic pathways utilized for the production of the desired compound, such as intermediates and side-products, to determine the overall efficiency of production of the compound. Analysis methods include measurements of nutrient levels in the medium (*e.g.*, sugars, hydrocarbons, nitrogen sources, phosphate, and other ions), measurements of biomass composition and growth, analysis of the production of common metabolites of biosynthetic pathways, and measurement of gasses produced during fermentation. Standard methods for these measurements are outlined in Applied Microbial Physiology, A Practical Approach, P.M. Rhodes and P.F. Stanbury, eds., IRL Press, p. 103-129; 131-163; and 165-192 (ISBN: 0199635773) and references cited therein.

Example 10: Purification of the Desired Product from *C. glutamicum* Culture

Recovery of the desired product from the *C. glutamicum* cells or supernatant of the above-described culture can be performed by various methods well known in the art. If the desired product is not secreted from the cells, the cells can be harvested from the culture by low-speed centrifugation, the cells can be lysed by standard techniques, such as mechanical force or sonication. The cellular debris is removed by centrifugation, and the supernatant fraction containing the soluble proteins is retained for further purification of the desired compound. If the product is secreted from the *C. glutamicum* cells, then the cells are removed from the culture by low-speed centrifugation, and the supernate fraction is retained for further purification.

The supernatant fraction from either purification method is subjected to chromatography with a suitable resin, in which the desired molecule is either retained on

a chromatography resin while many of the impurities in the sample are not, or where the impurities are retained by the resin while the sample is not. Such chromatography steps may be repeated as necessary, using the same or different chromatography resins. One of ordinary skill in the art would be well-versed in the selection of appropriate chromatography resins and in their most efficacious application for a particular molecule to be purified. The purified product may be concentrated by filtration or ultrafiltration, and stored at a temperature at which the stability of the product is maximized.

There are a wide array of purification methods known to the art and the preceding method of purification is not meant to be limiting. Such purification techniques are described, for example, in Bailey, J.E. & Ollis, D.F. Biochemical Engineering Fundamentals, McGraw-Hill: New York (1986).

The identity and purity of the isolated compounds may be assessed by techniques standard in the art. These include high-performance liquid chromatography (HPLC), spectroscopic methods, staining methods, thin layer chromatography, NIRS, enzymatic assay, or microbiologically. Such analysis methods are reviewed in: Patek *et al.* (1994) *Appl. Environ. Microbiol.* 60: 133-140; Malakhova *et al.* (1996) *Biotekhnologiya* 11: 27-32; and Schmidt *et al.* (1998) *Bioprocess Engineer.* 19: 67-70. Ulmann's Encyclopedia of Industrial Chemistry, (1996) vol. A27, VCH: Weinheim, p. 89-90, p. 521-540, p. 540-547, p. 559-566, 575-581 and p. 581-587; Michal, G. (1999) Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, John Wiley and Sons; Fallon, A. *et al.* (1987) Applications of HPLC in Biochemistry in: Laboratory Techniques in Biochemistry and Molecular Biology, vol. 17.

Example 11: Analysis of the Gene Sequences of the Invention

The comparison of sequences and determination of percent homology between two sequences are art-known techniques, and can be accomplished using a mathematical algorithm, such as the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci.* USA 87:2264-68, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci.* USA 90:5873-77. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to SMP nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to SMP protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped

BLAST programs, one of ordinary skill in the art will know how to optimize the parameters of the program (*e.g.*, XBLAST and NBLAST) for the specific sequence being analyzed.

Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Meyers and Miller ((1988) *Comput. Appl. Biosci.* 4: 11-17). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art, and include ADVANCE and ADAM. described in Torelli and Robotti (1994) *Comput. Appl. Biosci.* 10:3-5; and FASTA, described in Pearson and Lipman (1988) *P.N.A.S.* 85:2444-8.

The percent homology between two amino acid sequences can also be accomplished using the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. The percent homology between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package, using standard parameters, such as a gap weight of 50 and a length weight of 3.

A comparative analysis of the gene sequences of the invention with those present in Genbank has been performed using techniques known in the art (see, *e.g.*, Bexevanis and Ouellette, eds. (1998) Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins. John Wiley and Sons: New York). The gene sequences of the invention were compared to genes present in Genbank in a three-step process. In a first step, a BLASTN analysis (*e.g.*, a local alignment analysis) was performed for each of the sequences of the invention against the nucleotide sequences present in Genbank, and the top 500 hits were retained for further analysis. A subsequent FASTA search (*e.g.*, a combined local and global alignment analysis, in which limited regions of the sequences are aligned) was performed on these 500 hits. Each gene sequence of the invention was subsequently globally aligned to each of the top three FASTA hits, using the GAP program in the GCG software package (using standard parameters). In order to obtain correct results, the length of the sequences extracted from Genbank were adjusted to the length of the query sequences by methods well-known in the art. The results of this analysis are set forth in Table 4. The resulting data is identical to that which would have been obtained had a GAP (global) analysis alone been performed on each of the genes of the invention in comparison with each of the references in Genbank, but required significantly reduced computational time as compared to such a database-wide GAP

(global) analysis. Sequences of the invention for which no alignments above the cutoff values were obtained are indicated on Table 4 by the absence of alignment information. It will further be understood by one of ordinary skill in the art that the GAP alignment homology percentages set forth in Table 4 under the heading "% homology (GAP)" are listed in the European numerical format, wherein a ',' represents a decimal point. For example, a value of "40,345" in this column represents "40.345%".

Example 12: Construction and Operation of DNA Microarrays

The sequences of the invention may additionally be used in the construction and application of DNA microarrays (the design, methodology, and uses of DNA arrays are well known in the art, and are described, for example, in Schena, M. *et al.* (1995) *Science* 270: 467-470; Wodicka, L. *et al.* (1997) *Nature Biotechnology* 15: 1359-1367; DeSaizieu, A. *et al.* (1998) *Nature Biotechnology* 16: 45-48; and DeRisi, J.L. *et al.* (1997) *Science* 278: 680-686).

DNA microarrays are solid or flexible supports consisting of nitrocellulose, nylon, glass, silicone, or other materials. Nucleic acid molecules may be attached to the surface in an ordered manner. After appropriate labeling, other nucleic acids or nucleic acid mixtures can be hybridized to the immobilized nucleic acid molecules, and the label may be used to monitor and measure the individual signal intensities of the hybridized molecules at defined regions. This methodology allows the simultaneous quantification of the relative or absolute amount of all or selected nucleic acids in the applied nucleic acid sample or mixture. DNA microarrays, therefore, permit an analysis of the expression of multiple (as many as 6800 or more) nucleic acids in parallel (see, *e.g.*, Schena, M. (1996) *BioEssays* 18(5): 427-431).

The sequences of the invention may be used to design oligonucleotide primers which are able to amplify defined regions of one or more *C. glutamicum* genes by a nucleic acid amplification reaction such as the polymerase chain reaction. The choice and design of the 5' or 3' oligonucleotide primers or of appropriate linkers allows the covalent attachment of the resulting PCR products to the surface of a support medium described above (and also described, for example, Schena, M. *et al.* (1995) *Science* 270: 467-470).

Nucleic acid microarrays may also be constructed by *in situ* oligonucleotide synthesis as described by Wodicka, L. *et al.* (1997) *Nature Biotechnology* 15: 1359-1367. By photolithographic methods, precisely defined regions of the matrix are exposed to light. Protective groups which are photolabile are thereby activated and undergo nucleotide addition, whereas regions that are masked from light do not undergo any modification. Subsequent cycles of protection and light activation permit the

synthesis of different oligonucleotides at defined positions. Small, defined regions of the genes of the invention may be synthesized on microarrays by solid phase oligonucleotide synthesis.

The nucleic acid molecules of the invention present in a sample or mixture of nucleotides may be hybridized to the microarrays. These nucleic acid molecules can be labeled according to standard methods. In brief, nucleic acid molecules (*e.g.*, mRNA molecules or DNA molecules) are labeled by the incorporation of isotopically or fluorescently labeled nucleotides, *e.g.*, during reverse transcription or DNA synthesis. Hybridization of labeled nucleic acids to microarrays is described (*e.g.*, in Schena, M. *et al.* (1995) *supra*; Wodicka, L. *et al.* (1997), *supra*; and DeSaizieu A. *et al.* (1998), *supra*). The detection and quantification of the hybridized molecule are tailored to the specific incorporated label. Radioactive labels can be detected, for example, as described in Schena, M. *et al.* (1995) *supra*) and fluorescent labels may be detected, for example, by the method of Shalon *et al.* (1996) *Genome Research* 6: 639-645).

The application of the sequences of the invention to DNA microarray technology, as described above, permits comparative analyses of different strains of *C. glutamicum* or other Corynebacteria. For example, studies of inter-strain variations based on individual transcript profiles and the identification of genes that are important for specific and/or desired strain properties such as pathogenicity, productivity and stress tolerance are facilitated by nucleic acid array methodologies. Also, comparisons of the profile of expression of genes of the invention during the course of a fermentation reaction are possible using nucleic acid array technology.

Example 13: Analysis of the Dynamics of Cellular Protein Populations (Proteomics)

The genes, compositions, and methods of the invention may be applied to study the interactions and dynamics of populations of proteins, termed 'proteomics'. Protein populations of interest include, but are not limited to, the total protein population of *C. glutamicum* (*e.g.*, in comparison with the protein populations of other organisms), those proteins which are active under specific environmental or metabolic conditions (*e.g.*, during fermentation, at high or low temperature, or at high or low pH), or those proteins which are active during specific phases of growth and development.

Protein populations can be analyzed by various well-known techniques, such as gel electrophoresis. Cellular proteins may be obtained, for example, by lysis or extraction, and may be separated from one another using a variety of electrophoretic techniques. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) separates proteins largely on the basis of their molecular weight. Isoelectric focusing

polyacrylamide gel electrophoresis (IEF-PAGE) separates proteins by their isoelectric point (which reflects not only the amino acid sequence but also posttranslational modifications of the protein). Another, more preferred method of protein analysis is the consecutive combination of both IEF-PAGE and SDS-PAGE, known as 2-D-gel electrophoresis (described, for example, in Hermann *et al.* (1998) *Electrophoresis* 19: 3217-3221; Fountoulakis *et al.* (1998) *Electrophoresis* 19: 1193-1202; Langen *et al.* (1997) *Electrophoresis* 18: 1184-1192; Antelmann *et al.* (1997) *Electrophoresis* 18: 1451-1463). Other separation techniques may also be utilized for protein separation, such as capillary gel electrophoresis; such techniques are well known in the art.

Proteins separated by these methodologies can be visualized by standard techniques, such as by staining or labeling. Suitable stains are known in the art, and include Coomassie Brilliant Blue, silver stain, or fluorescent dyes such as Sypro Ruby (Molecular Probes). The inclusion of radioactively labeled amino acids or other protein precursors (*e.g.*, ^{35}S-methionine, ^{35}S-cysteine, ^{14}C-labelled amino acids, ^{15}N-amino acids, $^{15}NO_3$ or $^{15}NH_4^+$ or ^{13}C-labelled amino acids) in the medium of *C. glutamicum* permits the labeling of proteins from these cells prior to their separation. Similarly, fluorescent labels may be employed. These labeled proteins can be extracted, isolated and separated according to the previously described techniques.

Proteins visualized by these techniques can be further analyzed by measuring the amount of dye or label used. The amount of a given protein can be determined quantitatively using, for example, optical methods and can be compared to the amount of other proteins in the same gel or in other gels. Comparisons of proteins on gels can be made, for example, by optical comparison, by spectroscopy, by image scanning and analysis of gels, or through the use of photographic films and screens. Such techniques are well-known in the art.

To determine the identity of any given protein, direct sequencing or other standard techniques may be employed. For example, N- and/or C-terminal amino acid sequencing (such as Edman degradation) may be used, as may mass spectrometry (in particular MALDI or ESI techniques (see, *e.g.*, Langen *et al.* (1997) *Electrophoresis* 18: 1184-1192)). The protein sequences provided herein can be used for the identification of *C. glutamicum* proteins by these techniques.

The information obtained by these methods can be used to compare patterns of protein presence, activity, or modification between different samples from various biological conditions (*e.g.*, different organisms, time points of fermentation, media conditions, or different biotopes, among others). Data obtained from such experiments alone, or in combination with other techniques, can be used for various applications, such as to compare the behavior of various organisms in a given (*e.g.*, metabolic)

situation, to increase the productivity of strains which produce fine chemicals or to increase the efficiency of the production of fine chemicals.

Equivalents

Those of ordinary skill in the art will recognize, or will be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

TABLE 1: GENES IN THE APPLICATION

HMP:

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
1	2	RXS02735	VV0074	14576	15280	6-Phosphoglucolactonase
3	4	RXA01626	GR00452	4270	3926	L-ribulose-phosphate 4-epimerase
5	6	RXA02245	GR00654	13639	14295	RIBULOSE-PHOSPHATE 3-EPIMERASE (EC 5.1.3.1)
7	8	RXA01015	GR00290	346	5	RIBOSE 5-PHOSPHATE ISOMERASE (EC 5.3.1.6)

TCA:

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
9	10	RXN01312	VV0082	20803	18785	SUCCINATE DEHYDROGENASE FLAVOPROTEIN SUBUNIT (EC 1.3.99.1)
11	12	F RXA01312	GR00380	2690	1614	SUCCINATE DEHYDROGENASE FLAVOPROTEIN SUBUNIT (EC 1.3.99.1)
13	14	RXN00231	VV0083	15484	14015	SUCCINATE-SEMIALDEHYDE DEHYDROGENASE (NADP+) (EC 1.2.1.16)
15	16	RXA01311	GR00380	1611	865	SUCCINATE DEHYDROGENASE IRON-SULFUR PROTEIN (EC 1.3.99.1)
17	18	RXA01535	GR00427	1354	2760	FUMARATE HYDRATASE PRECURSOR (EC 4.2.1.2)
19	20	RXA00517	GR00131	1407	2447	MALATE DEHYDROGENASE (EC 1.1.1.37) (EC 1.1.1.82)
21	22	RXA01350	GR00392	1844	2827	MALATE DEHYDROGENASE (EC 1.1.1.37)

EMB-Pathway

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
23	24	RXA02149	GR00639	17786	18754	GLUCOKINASE (EC 2.7.1.2)
25	26	RXA01814	GR00515	2571	910	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
27	28	RXN02803	VV0086	1	657	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
29	30	F RXA02803	GR00784	2	400	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
31	32	RXN03076	VV0043	1624	35	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
33	34	F RXA02854	GR10002	1588	5	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
35	36	RXA00511	GR00129	1	513	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
37	38	RXN01365	VV0091	1476	103	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
39	40	F RXA01365	GR00397	897	4	PHOSPHOGLUCOMUTASE (EC 5.4.2.2) / PHOSPHOMANNOMUTASE (EC 5.4.2.8)
41	42	RXA00098	GR00014	6525	8144	GLUCOSE-6-PHOSPHATE ISOMERASE (GPI) (EC 5.3.1.9)
43	44	RXA01989	GR00578	1	630	GLUCOSE-6-PHOSPHATE ISOMERASE A (GPI A) (EC 5.3.1.9)
45	46	RXA00340	GR00059	1549	2694	PHOSPHOGLYCERATE MUTASE (EC 5.4.2.1)
47	48	RXA02492	GR00720	2201	2917	PHOSPHOGLYCERATE MUTASE (EC 5.4.2.1)
49	50	RXA00381	GR00082	1451	846	PHOSPHOGLYCERATE MUTASE (EC 5.4.2.1)
51	52	RXA02122	GR00636	6511	5813	PHOSPHOGLYCERATE MUTASE (EC 5.4.2.1)
53	54	RXA00206	GR00032	6171	5134	6-PHOSPHOFRUCTOKINASE (EC 2.7.1.11)
55	56	RXA01243	GR00359	2302	3261	1-PHOSPHOFRUCTOKINASE (EC 2.7.1.56)
57	58	RXA01882	GR00538	1165	2154	1-PHOSPHOFRUCTOKINASE (EC 2.7.1.56)
59	60	RXA01702	GR00479	1397	366	FRUCTOSE-BISPHOSPHATE ALDOLASE (EC 4.1.2.13)
61	62	RXA02258	GR00654	26451	27227	TRIOSEPHOSPHATE ISOMERASE (EC 5.3.1.1)
63	64	RXN01225	VV0064	6382	4943	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12)
65	66	F RXA01225	GR00354	5302	6741	GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE HOMOLOG
67	68	RXA02256	GR00654	23934	24935	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12)
69	70	RXA02257	GR00654	25155	26369	PHOSPHOGLYCERATE KINASE (EC 2.7.2.3)
71	72	RXA00235	GR00036	2365	1091	ENOLASE (EC 4.2.1.11)
73	74	RXA01093	GR00306	1552	122	PYRUVATE KINASE (EC 2.7.1.40)
75	76	RXN02675	VV0098	72801	70945	PYRUVATE KINASE (EC 2.7.1.40)
77	78	F RXA02675	GR00754	2	364	PYRUVATE KINASE (EC 2.7.1.40)
79	80	F RXA02695	GR00755	2949	4370	PYRUVATE KINASE (EC 2.7.1.40)
81	82	RXA00682	GR00179	5299	3401	PHOSPHOENOLPYRUVATE SYNTHASE (EC 2.7.9.2)
83	84	RXA00683	GR00179	6440	5349	PHOSPHOENOLPYRUVATE SYNTHASE (EC 2.7.9.2)
85	86	RXN00635	VV0135	22708	20972	PYRUVATE DEHYDROGENASE (CYTOCHROME) (EC 1.2.2.2)
87	88	F RXA02807	GR00788	88	552	PYRUVATE DEHYDROGENASE (CYTOCHROME) (EC 1.2.2.2)
89	90	F RXA00635	GR00167	3	923	PYRUVATE DEHYDROGENASE (CYTOCHROME) (EC 1.2.2.2)
91	92	RXN03044	VV0019	1391	2221	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
93	94	F RXA02852	GR00852	3	281	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
95	96	F RXA00268	GR00041	125	955	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
97	98	RXN03086	VV0049	2243	2650	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
99	100	F RXA02887	GR10022	411	4	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
101	102	RXN03043	VV0019	1	1362	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
103	104	F RXA02897	GR10039	1291	5	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
105	106	RXN03083	VV0047	88	1110	DIHYDROLIPOAMIDE DEHYDROGENASE (EC 1.8.1.4)
107	108	F RXA02853	GR10001	89	1495	DIHYDROLIPOAMIDE DEHYDROGENASE (EC 1.8.1.4)
109	110	RXA02259	GR00654	27401	30172	PHOSPHOENOLPYRUVATE CARBOXYLASE (EC 4.1.1.31)
111	112	RXN02326	VV0047	4500	5315	PYRUVATE CARBOXYLASE (EC 6.4.1.1)
113	114	F RXA02326	GR00668	5338	4523	PYRUVATE CARBOXYLASE
115	116	RXN02327	VV0047	3533	4492	PYRUVATE CARBOXYLASE (EC 6.4.1.1)
117	118	F RXA02327	GR00668	6305	5346	PYRUVATE CARBOXYLASE
119	120	RXN02328	VV0047	1842	3437	PYRUVATE CARBOXYLASE (EC 6.4.1.1)
121	122	F RXA02328	GR00668	7783	6401	PYRUVATE CARBOXYLASE (EC 6.4.1.1)
123	124	RXN01048	VV0079	12539	11316	MALIC ENZYME (EC 1.1.1.39)

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
125	126	F RXA01048	GR00296	3	290	MALIC ENZYME (EC 1.1.1.39)
127	128	F RXA00290	GR00046	4693	5655	MALIC ENZYME (EC 1.1.1.39)
129	130	RXA02694	GR00755	1879	2820	L-LACTATE DEHYDROGENASE (EC 1.1.1.27)
131	132	RXN00296	VV0176	35763	38606	D-LACTATE DEHYDROGENASE (CYTOCHROME) (EC 1.1.2.4)
133	134	F RXA00296	GR00048	3	2837	D-LACTATE DEHYDROGENASE (CYTOCHROME) (EC 1.1.2.4)
135	136	RXA01901	GR00544	4158	5417	L-LACTATE DEHYDROGENASE (CYTOCHROME) (EC 1.1.2.3)
137	138	RXN01952	VV0105	9954	11666	D-LACTATE DEHYDROGENASE (EC 1.1.1.28)
139	140	F RXA01952	GR00562	1	216	D-LACTATE DEHYDROGENASE (EC 1.1.1.28)
141	142	F RXA01955	GR00562	4611	6209	D-LACTATE DEHYDROGENASE (EC 1.1.1.28)
143	144	RXA00293	GR00047	2645	1734	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
145	146	RXN01130	VV0157	6138	5536	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
147	148	F RXA01130	GR00315	2	304	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
149	150	RXN03112	VV0085	509	6	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
151	152	F RXA01133	GR00316	568	1116	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
153	154	RXN00871	VV0127	3127	2240	IOLB PROTEIN
155	156	F RXA00871	GR00239	2344	3207	IOLB PROTEIN: D-FRUCTOSE 1,6-BISPHOSPHATE = GLYCERONE-CC PHOSPHATE + D- GLYCERALDEHYDE 3-PHOSPHATE.
157	158	RXN02829	VV0354	287	559	IOLS PROTEIN
159	160	F RXA02829	GR00816	287	562	IOLS PROTEIN
161	162	RXN01468	VV0019	7474	8298	NAGD PROTEIN
163	164	F RXA01468	GR00422	1250	2074	PUTATIVE N-GLYCERALDEHYDE-2-PHOSPHOTRANSFERASE
165	166	RXA00794	GR00211	3993	2989	GLPX PROTEIN
167	168	RXN02920	VV0213	6135	5224	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
169	170	F RXA02379	GR00690	1390	686	D-3-PHOSPHOGLYCERATE DEHYDROGENASE (EC 1.1.1.95)
171	172	RXN02688	VV0098	59053	58385	PHOSPHOGLYCERATE MUTASE (EC 5.4.2.1)
173	174	RXN03087	VV0052	3216	3428	PYRUVATE CARBOXYLASE (EC 6.4.1.1)
175	176	RXN03186	VV0377	310	519	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
177	178	RXN03187	VV0382	3	281	PYRUVATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.1)
179	180	RXN02591	VV0098	14370	12541	PHOSPHOENOLPYRUVATE CARBOXYKINASE [GTP] (EC 4.1.1.32)
181	182	RXS01260	VV0009	3477	2296	LIPOAMIDE DEHYDROGENASE COMPONENT (E3) OF BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE COMPLEX (EC 1.8.1.4)
183	184	RXS01261	VV0009	3703	3533	LIPOAMIDE DEHYDROGENASE COMPONENT (E3) OF BRANCHED-CHAIN ALPHA-KETO ACID DEHYDROGENASE COMPLEX (EC 1.8.1.4)

Glycerol metabolism

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
185	186	RXA02640	GR00749	1400	2926	GLYCEROL KINASE (EC 2.7.1.30)
187	188	RXN01025	VV0143	5483	4488	GLYCEROL-3-PHOSPHATE DEHYDROGENASE (NAD(P)+) (EC 1.1.1.94)
189	190	F RXA01025	GR00293	939	1853	GLYCEROL-3-PHOSPHATE DEHYDROGENASE (NAD(P)+) (EC 1.1.1.94)
191	192	RXA01851	GR00525	3515	1830	AEROBIC GLYCEROL-3-PHOSPHATE DEHYDROGENASE (EC 1.1.99.5)
193	194	RXA01242	GR00359	1526	2302	GLYCEROL-3-PHOSPHATE REGULON REPRESSOR
195	196	RXA02288	GR00661	992	147	GLYCEROL-3-PHOSPHATE REGULON REPRESSOR

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
197	198	RXN01891	VV0122	24949	24086	GLYCEROL-3-PHOSPHATE-BINDING PERIPLASMIC PROTEIN PRECURSOR
199	200	F RXA01891	GR00541	1736	918	GLYCEROL-3-PHOSPHATE-BINDING PERIPLASMIC PROTEIN PRECURSOR
201	202	RXA02414	GR00703	3808	3062	Uncharacterized protein involved in glycerol metabolism (homolog of Drosophila rhomboid)
203	204	RXN01580	VV0122	22091	22807	Glycerophosphoryl diester phosphodiesterase

Acetate metabolism

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
205	206	RXA01436	GR00418	2547	1357	ACETATE KINASE (EC 2.7.2.1)
207	208	RXA00686	GR00179	8744	7941	ACETATE OPERON REPRESSOR
209	210	RXA00246	GR00037	4425	3391	ALCOHOL DEHYDROGENASE (EC 1.1.1.1)
211	212	RXA01571	GR00438	1360	1959	ALCOHOL DEHYDROGENASE (EC 1.1.1.1)
213	214	RXA01572	GR00438	1928	2419	ALCOHOL DEHYDROGENASE (EC 1.1.1.1)
215	216	RXA01758	GR00498	3961	2945	ALCOHOL DEHYDROGENASE (EC 1.1.1.1)
217	218	RXA02539	GR00726	11676	10159	ALDEHYDE DEHYDROGENASE (EC
219	220	RXN03061	VV0034	108	437	ALDEHYDE DEHYDROGENASE (EC 1.2.1.3)
221	222	RXN03150	VV0155	10678	10055	ALDEHYDE DEHYDROGENASE (EC 1.2.1.3)
223	224	RXN01340	VV0033	3	860	ALDEHYDE DEHYDROGENASE (EC 1.2.1.3)
225	226	RXN01498	VV0008	1598	3160	ALDEHYDE DEHYDROGENASE (EC 1.2.1.3)
227	228	RXN02674	VV0315	15614	14163	ALDEHYDE DEHYDROGENASE (EC 1.2.1.3)
229	230	RXN00868	VV0127	2230	320	ACETOLACTATE SYNTHASE LARGE SUBUNIT (EC 4.1.3.18)
231	232	RXN01143	VV0077	9372	8254	ACETOLACTATE SYNTHASE LARGE SUBUNIT (EC 4.1.3.18)
233	234	RXN01146	VV0264	243	935	ACETOLACTATE SYNTHASE LARGE SUBUNIT (EC 4.1.3.18)
235	236	RXN01144	VV0077	8237	7722	ACETOLACTATE SYNTHASE SMALL SUBUNIT (EC 4.1.3.18)

Butanediol, diacetyl and acetoin formation

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
237	238	RXA02474	GR00715	8082	7309	(S,S)-butane-2,3-diol dehydrogenase (EC 1.1.1.76)
239	240	RXA02453	GR00710	6103	5351	ACETOIN(DIACETYL) REDUCTASE (EC 1.1.1.5)
241	242	RXS01758	VV0112	27383	28399	ALCOHOL DEHYDROGENASE (EC 1.1.1.1)

HMP-Cycle

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
243	244	RXA02737	GR00763	3312	1771	GLUCOSE-6-PHOSPHATE 1-DEHYDROGENASE (EC 1.1.1.49)
245	246	RXA02738	GR00763	4499	3420	TRANSALDOLASE (EC 2.2.1.2)
247	248	RXA02739	GR00763	6769	4670	TRANSKETOLASE (EC 2.2.1.1)
249	250	RXA00965	GR00270	1232	510	6-PHOSPHOGLUCONATE DEHYDROGENASE, DECARBOXYLATING (EC 1.1.1.44)
251	252	RXN00999	VV0106	2817	1366	6-PHOSPHOGLUCONATE DEHYDROGENASE, DECARBOXYLATING (EC 1.1.1.44)
253	254	F RXA00999	GR00283	3012	4448	6-PHOSPHOGLUCONATE DEHYDROGENASE, DECARBOXYLATING (EC 1.1.1.44)

Nucleotide sugar conversion

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
255	256	RXN02596	VV0098	48784	47582	UDP-GALACTOPYRANOSE MUTASE (EC 5.4.99.9)
257	258	F RXA02596	GR00742	1	489	UDP-GALACTOPYRANOSE MUTASE (EC 5.4.99.9)
259	260	F RXA02642	GR00749	5383	5880	UDP-GALACTOPYRANOSE MUTASE (EC 5.4.99.9)
261	262	RXA02572	GR00737	2	646	UDP-GLUCOSE 6-DEHYDROGENASE (EC 1.1.1.22)
263	264	RXA02485	GR00718	2345	3445	UDP-N-ACETYLENOLPYRUVOYLGLUCOSAMINE REDUCTASE (EC 1.1.1.158)
265	266	RXA01216	GR00352	2302	1202	UDP-N-ACETYLGLUCOSAMINE PYROPHOSPHORYLASE (EC 2.7.7.23)
267	268	RXA01259	GR00367	987	130	UTP--GLUCOSE-1-PHOSPHATE URIDYLYLTRANSFERASE (EC 2.7.7.9)
269	270	RXA02028	GR00616	573	998	UTP--GLUCOSE-1-PHOSPHATE URIDYLYLTRANSFERASE (EC 2.7.7.9)
271	272	RXA01262	GR00367	8351	7191	GDP-MANNOSE 6-DEHYDROGENASE (EC 1.1.1.132)
273	274	RXA01377	GR00400	3935	5020	MANNOSE-1-PHOSPHATE GUANYLTRANSFERASE (EC 2.7.7.13)
275	276	RXA02063	GR00626	3301	4527	GLUCOSE-1-PHOSPHATE ADENYLYLTRANSFERASE (EC 2.7.7.27)
277	278	RXN00014	VV0048	8848	9627	GLUCOSE-1-PHOSPHATE THYMIDYLYLTRANSFERASE (EC 2.7.7.24)
279	280	F RXA00014	GR00002	4448	5227	GLUCOSE-1-PHOSPHATE THYMIDYLYLTRANSFERASE (EC 2.7.7.24)
281	282	RXA01570	GR00438	427	1281	GLUCOSE-1-PHOSPHATE THYMIDYLYLTRANSFERASE (EC 2.7.7.24)
283	284	RXA02666	GR00753	7260	6493	D-RIBITOL-5-PHOSPHATE CYTIDYLYLTRANSFERASE (EC 2.7.7.40)
285	286	RXA00825	GR00222	222	1154	DTDP-GLUCOSE 4,6-DEHYDRATASE (EC 4.2.1.46)

Inositol and ribitol metabolism

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
287	288	RXA01887	GR00539	4219	3209	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
289	290	RXN00013	VV0048	7966	8838	MYO-INOSITOL-1(OR 4)-MONOPHOSPHATASE 1 (EC 3.1.3.25)
291	292	F RXA00013	GR00002	3566	4438	MYO-INOSITOL-1(OR 4)-MONOPHOSPHATASE 1 (EC 3.1.3.25)
293	294	RXA01099	GR00306	6328	5504	INOSITOL MONOPHOSPHATE PHOSPHATASE
295	296	RXN01332	VV0273	579	4	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
297	298	F RXA01332	GR00388	552	4	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
299	300	RXA01632	GR00454	2338	3342	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
301	302	RXA01633	GR00454	3380	4462	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
303	304	RXN01406	VV0278	2999	1977	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
305	306	RXN01630	VV0050	48113	47037	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
307	308	RXN00528	VV0079	23406	22318	MYO-INOSITOL-1-PHOSPHATE SYNTHASE (EC 5.5.1.4)
309	310	RXN03057	VV0028	7017	7688	MYO-INOSITOL 2-DEHYDROGENASE (EC 1.1.1.18)
311	312	F RXA02902	GR10040	10277	10948	GLUCOSE-FRUCTOSE OXIDOREDUCTASE PRECURSOR (EC 1.1.99.28)
313	314	RXA00251	GR00038	931	224	RIBITOL 2-DEHYDROGENASE (EC 1.1.1.56)

Utilization of sugars

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
315	316	RXN02654	VV0090	12206	13090	GLUCOSE 1-DEHYDROGENASE (EC 1.1.1.47)
317	318	F RXA02654	GR00752	7405	8289	GLUCOSE 1-DEHYDROGENASE II (EC 1.1.1.47)
319	320	RXN01049	VV0079	9633	11114	GLUCONOKINASE (EC 2.7.1.12)
321	322	F RXA01049	GR00296	1502	492	GLUCONOKINASE (EC 2.7.1.12)
323	324	F RXA01050	GR00296	1972	1499	GLUCONOKINASE (EC 2.7.1.12)
325	326	RXA00202	GR00032	1216	275	D-RIBOSE-BINDING PERIPLASMIC PROTEIN PRECURSOR
327	328	RXN00872	VV0127	6557	5604	FRUCTOKINASE (EC 2.7.1.4)
329	330	F RXA00872	GR00240	565	1086	FRUCTOKINASE (EC 2.7.1.4)
331	332	RXN00799	VV0009	58477	56834	PERIPLASMIC BETA-GLUCOSIDASE/BETA-XYLOSIDASE PRECURSOR (EC 3.2.1.21) (EC 3.2.1.37)
333	334	F RXA00799	GR00214	1	1584	PERIPLASMIC BETA-GLUCOSIDASE/BETA-XYLOSIDASE PRECURSOR (EC 3.2.1.21) (EC 3.2.1.37)
335	336	RXA00032	GR00003	12028	10520	MANNITOL 2-DEHYDROGENASE (EC 1.1.1.67)
337	338	RXA02528	GR00725	6880	7854	FRUCTOSE REPRESSOR
339	340	RXN00316	VV0006	7035	8180	Hypothetical Oxidoreductase (EC 1.1.1.-)
341	342	F RXA00309	GR00053	316	5	GLUCOSE--FRUCTOSE OXIDOREDUCTASE PRECURSOR (EC 1.1.99.28)
343	344	RXN00310	VV0006	6616	7050	GLUCOSE--FRUCTOSE OXIDOREDUCTASE PRECURSOR (EC 1.1.99.28)
345	346	F RXA00310	GR00053	735	301	GLUCOSE--FRUCTOSE OXIDOREDUCTASE PRECURSOR (EC 1.1.99.28)
347	348	RXA00041	GR00007	1246	5	SUCROSE-6-PHOSPHATE HYDROLASE (EC 3.2.1.26)
349	350	RXA02026	GR00615	725	6	SUCROSE-6-PHOSPHATE HYDROLASE (EC 3.2.1.26)
351	352	RXA02061	GR00626	1842	349	SUCROSE-6-PHOSPHATE HYDROLASE (EC 3.2.1.26)
353	354	RXN01369	VV0124	595	1776	MANNOSE-6-PHOSPHATE ISOMERASE (EC 5.3.1.8)

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
355	356	F RXA01369	GR00398	3	503	MANNOSE-6-PHOSPHATE ISOMERASE (EC 5.3.1.8)
357	358	F RXA01373	GR00399	595	1302	MANNOSE-6-PHOSPHATE ISOMERASE (EC 5.3.1.8)
359	360	RXA02611	GR00743	1	1752	1,4-ALPHA-GLUCAN BRANCHING ENZYME (EC 2.4.1.18)
361	362	RXA02612	GR00743	1793	3985	1,4-ALPHA-GLUCAN BRANCHING ENZYME (EC 2.4.1.18)
363	364	RXN01884	VV0184	1	1890	GLYCOGEN DEBRANCHING ENZYME (EC 2.4.1.25) (EC 3.2.1.33)
365	366	F RXA01884	GR00539	3	1475	GLYCOGEN DEBRANCHING ENZYME (EC 2.4.1.25) (EC 3.2.1.33)
367	368	RXA01111	GR00306	16981	17427	GLYCOGEN OPERON PROTEIN GLGX (EC 3.2.1.-)
369	370	RXN01550	VV0143	14749	16260	GLYCOGEN PHOSPHORYLASE (EC 2.4.1.1)
371	372	F RXA01550	GR00431	3	1346	GLYCOGEN PHOSPHORYLASE (EC 2.4.1.1)
373	374	RXN02100	VV0318	2	2326	GLYCOGEN PHOSPHORYLASE (EC 2.4.1.1)
375	376	F RXA02100	GR00631	3	920	GLYCOGEN PHOSPHORYLASE (EC 2.4.1.1)
377	378	F RXA02113	GR00633	2	1207	GLYCOGEN PHOSPHORYLASE (EC 2.4.1.1)
379	380	RXA02147	GR00639	15516	16532	ALPHA-AMYLASE (EC 3.2.1.1)
381	382	RXA01478	GR00422	10517	12352	GLUCOAMYLASE G1 AND G2 PRECURSOR (EC 3.2.1.3)
383	384	RXA01888	GR00539	4366	4923	GLUCOSE-RESISTANCE AMYLASE REGULATOR
385	386	RXN01927	VV0127	50623	49244	XYLULOSE KINASE (EC 2.7.1.17)
387	388	F RXA01927	GR00555	3	1118	XYLULOSE KINASE (EC 2.7.1.17)
389	390	RXA02729	GR00762	747	4	RIBOKINASE (EC 2.7.1.15)
391	392	RXA02797	GR00778	1739	2641	RIBOKINASE (EC 2.7.1.15)
393	394	RXA02730	GR00762	1768	731	RIBOSE OPERON REPRESSOR
395	396	RXA02551	GR00729	2193	2552	6-PHOSPHO-BETA-GLUCOSIDASE (EC 3.2.1.86)
397	398	RXA01325	GR00385	5676	5005	DEOXYRIBOSE-PHOSPHATE ALDOLASE (EC 4.1.2.4)
399	400	RXA00195	GR00030	543	1103	1-deoxy-D-xylulose 5-phosphate reductoisomerase (EC 1.1.1.-)
401	402	RXA00196	GR00030	1094	1708	1-deoxy-D-xylulose 5-phosphate reductoisomerase (EC 1.1.1.-)
403	404	RXN01562	VV0191	1230	3137	1-DEOXYXYLULOSE-5-PHOSPHATE SYNTHASE
405	406	F RXA01562	GR00436	2	1039	1-DEOXYXYLULOSE-5-PHOSPHATE SYNTHASE
407	408	F RXA01705	GR00480	971	1573	1-DEOXYXYLULOSE-5-PHOSPHATE SYNTHASE
409	410	RXN00879	VV0099	8763	6646	4-ALPHA-GLUCANOTRANSFERASE (EC 2.4.1.25)
411	412	F RXA00879	GR00242	5927	3828	4-ALPHA-GLUCANOTRANSFERASE (EC 2.4.1.25), amylomaltase
413	414	RXN00043	VV0119	3244	2081	N-ACETYLGLUCOSAMINE-6-PHOSPHATE DEACETYLASE (EC 3.5.1.25)
415	416	F RXA00043	GR00007	3244	2081	N-ACETYLGLUCOSAMINE-6-PHOSPHATE DEACETYLASE (EC 3.5.1.25)
417	418	RXN01752	VV0127	35265	33805	N-ACETYLGLUCOSAMINYLTRANSFERASE (EC 2.4.1.-)
419	420	F RXA01839	GR00520	1157	510	N-ACETYLGLUCOSAMINYLTRANSFERASE (EC 2.4.1.-)
421	422	RXA01859	GR00529	1473	547	N-ACETYLGLUCOSAMINYLTRANSFERASE (EC 2.4.1.-)
423	424	RXA00042	GR00007	2037	1279	GLUCOSAMINE-6-PHOSPHATE ISOMERASE (EC 5.3.1.10)
425	426	RXA01482	GR00422	17271	15397	GLUCOSAMINE--FRUCTOSE-6-PHOSPHATE AMINOTRANSFERASE (ISOMERIZING) (EC 2.6.1.16)
427	428	RXN03179	VV0336	2	667	URONATE ISOMERASE (EC 5.3.1.12)
429	430	F RXA02872	GR10013	675	4	URONATE ISOMERASE, Glucuronate isomerase (EC 5.3.1.12)
431	432	RXN03180	VV0337	672	163	URONATE ISOMERASE (EC 5.3.1.12)
433	434	F RXA02873	GR10014	672	163	URONATE ISOMERASE, Glucuronate isomerase (EC 5.3.1.12)
435	436	RXA02292	GR00662	1611	2285	GALACTOSIDE O-ACETYLTRANSFERASE (EC 2.3.1.18)
437	438	RXA02666	GR00753	7260	6493	D-RIBITOL-5-PHOSPHATE CYTIDYLYLTRANSFERASE (EC 2.7.7.40)
439	440	RXA00202	GR00032	1216	275	D-RIBOSE-BINDING PERIPLASMIC PROTEIN PRECURSOR
441	442	RXA02440	GR00709	5097	4258	D-RIBOSE-BINDING PERIPLASMIC PROTEIN PRECURSOR
443	444	RXN01569	VV0009	41086	42444	dTDP-4-DEHYDRORHAMNOSE REDUCTASE (EC 1.1.1.133)

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
445	446	F RXA01569	GR00438	2	427	DTDP-4-DEHYDRORHAMNOSE REDUCTASE (EC 1.1.1.133)
447	448	F RXA02055	GR00624	7122	8042	DTDP-4-DEHYDRORHAMNOSE REDUCTASE (EC 1.1.1.133)
449	450	RXA00825	GR00222	222	1154	DTDP-GLUCOSE 4,6-DEHYDRATASE (EC 4.2.1.46)
451	452	RXA02054	GR00624	6103	7119	DTDP-GLUCOSE 4,6-DEHYDRATASE (EC 4.2.1.46)
453	454	RXN00427	VV0112	7004	6219	dTDP-RHAMNOSYL TRANSFERASE RFBF (EC 2.-.-.-)
455	456	F RXA00427	GR00098	1591	2022	DTDP-RHAMNOSYL TRANSFERASE RFBF (EC 2.-.-.-)
457	458	RXA00327	GR00057	10263	9880	PROTEIN ARAJ
459	460	RXA00328	GR00057	11147	10656	PROTEIN ARAJ
461	462	RXA00329	GR00057	12390	11167	PROTEIN ARAJ
463	464	RXN01554	VV0135	28686	26545	GLUCAN ENDO-1,3-BETA-GLUCOSIDASE A1 PRECURSOR (EC 3.2.1.39)
465	466	RXN03015	VV0063	289	8	UDP-GLUCOSE 6-DEHYDROGENASE (EC 1.1.1.22)
467	468	RXN03056	VV0028	6258	6935	PUTATIVE HEXULOSE-6-PHOSPHATE ISOMERASE (EC 5.-.-.-)
469	470	RXN03030	VV0009	57006	56443	PERIPLASMIC BETA-GLUCOSIDASE/BETA-XYLOSIDASE PRECURSOR (EC 3.2.1.21) (EC 3.2.1.37)
471	472	RXN00401	VV0025	12427	11489	5-DEHYDRO-4-DEOXYGLUCARATE DEHYDRATASE (EC 4.2.1.41)
473	474	RXN02125	VV0102	23242	22442	ALDOSE REDUCTASE (EC 1.1.1.21)
475	476	RXN00200	VV0181	1679	5116	arabinosyl transferase subunit B (EC 2.4.2.-)
477	478	RXN01175	VV0017	39688	38303	PHOSPHO-2-DEHYDRO-3-DEOXYHEPTONATE ALDOLASE (EC 4.1.2.15)
479	480	RXN01376	VV0091	5610	4750	PUTATIVE GLYCOSYL TRANSFERASE WBIF
481	482	RXN01631	VV0050	47021	46143	PUTATIVE HEXULOSE-6-PHOSPHATE ISOMERASE (EC 5.-.-.-)
483	484	RXN01593	VV0229	13274	12408	NAGD PROTEIN
485	486	RXN00337	VV0197	20369	21418	GALACTOKINASE (EC 2.7.1.6)
487	488	RXS00584	VV0323	5516	6640	PHOSPHO-2-DEHYDRO-3-DEOXYHEPTONATE ALDOLASE (EC 4.1.2.15)
489	490	RXS02574				BETA-HEXOSAMINIDASE A PRECURSOR (EC 3.2.1.52)
491	492	RXS03215				GLUCOSE--FRUCTOSE OXIDOREDUCTASE PRECURSOR (EC 1.1.99.28)
493	494	F RXA01915	GR00549	1	1008	GLUCOSE--FRUCTOSE OXIDOREDUCTASE PRECURSOR (EC 1.1.99.28)
495	496	RXS03224				CYCLOMALTODEXTRINASE (EC 3.2.1.54)
497	498	F RXA00038	GR00006	1417	260	CYCLOMALTODEXTRINASE (EC 3.2.1.54)
499	500	RXC00233				protein involved in sugar metabolism
501	502	RXC00236				Membrane Lipoprotein involved in sugar metabolism
503	504	RXC00271				Exported Protein involved in ribose metabolism
505	506	RXC00338				protein involved in sugar metabolism
507	508	RXC00362				Membrane Spanning Protein involved in metabolism of diols
509	510	RXC00412				Amino Acid ABC Transporter ATP-Binding Protein involved in sugar metabolism
511	512	RXC00526				ABC Transporter ATP-Binding Protein involved in sugar metabolism
513	514	RXC01004				Membrane Spanning Protein involved in sugar metabolism
515	516	RXC01017				Cytosolic Protein involved in sugar metabolism
517	518	RXC01021				Cytosolic Kinase involved in metabolism of sugars and thiamin
519	520	RXC01212				ABC Transporter ATP-Binding Protein involved in sugar metabolism
521	522	RXC01306				Membrane Spanning Protein involved in sugar metabolism
523	524	RXC01366				Cytosolic Protein involved in sugar metabolism
525	526	RXC01372				Cytosolic Protein involved in sugar metabolism
527	528	RXC01659				protein involved in sugar metabolism

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
529	530	RXC01663				protein involved in sugar metabolism
531	532	RXC01693				protein involved in sugar metabolism
533	534	RXC01703				Cytosolic Protein involved in sugar metabolism
535	536	RXC02254				Membrane Associated Protein involved in sugar metabolism
537	538	RXC02255				Cytosolic Protein involved in sugar metabolism
539	540	RXC02435				protein involved in sugar metabolism
541	542	F RXA02435	GR00709	825	268	Uncharacterized protein involved in glycerol metabolism (homolog of Drosophila rhomboid)
543	544	RXC03216				protein involved in sugar metabolism

TCA-cycle

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
545	546	RXA02175	GR00641	10710	9418	CITRATE SYNTHASE (EC 4.1.3.7)
547	548	RXA02621	GR00746	2647	1829	CITRATE LYASE BETA CHAIN (EC 4.1.3.6)
549	550	RXN00519	VV0144	5585	3372	ISOCITRATE DEHYDROGENASE (NADP) (EC 1.1.1.42)
551	552	F RXA00521	GR00133	2	1060	ISOCITRATE DEHYDROGENASE [NADP] (EC 1.1.1.42)
553	554	RXN02209	VV0304	1	1671	ACONITATE HYDRATASE (EC 4.2.1.3)
555	556	F RXA02209	GR00648	3	1661	ACONITATE HYDRATASE (EC 4.2.1.3)
557	558	RXN02213	VV0305	1378	2151	ACONITATE HYDRATASE (EC 4.2.1.3)
559	560	F RXA02213	GR00649	1330	2046	ACONITATE HYDRATASE (EC 4.2.1.3)
561	562	RXA02056	GR00625	3	2870	2-OXOGLUTARATE DEHYDROGENASE E1 COMPONENT (EC 1.2.4.2)
563	564	RXA01745	GR00495	2	1495	DIHYDROLIPOAMIDE SUCCINYLTRANSFERASE COMPONENT (E2) OF 2-OXOGLUTARATE DEHYDROGENASE COMPLEX (EC 2.3.1.61)
565	566	RXA00782	GR00206	3984	3103	SUCCINYL-COA SYNTHETASE ALPHA CHAIN (EC 6.2.1.5)
567	568	RXA00783	GR00206	5280	4009	SUCCINYL-COA SYNTHETASE BETA CHAIN (EC 6.2.1.5)
569	570	RXN01695	VV0139	11307	12806	L-MALATE DEHYDROGENASE (ACCEPTOR) (EC 1.1.99.16)
571	572	F RXA01615	GR00449	8608	9546	L-MALATE DEHYDROGENASE (ACCEPTOR) (EC 1.1.99.16)
573	574	F RXA01695	GR00474	4388	4179	L-MALATE DEHYDROGENASE (ACCEPTOR) (EC 1.1.99.16)
575	576	RXA00290	GR00046	4693	5655	MALIC ENZYME (EC 1.1.1.39)
577	578	RXN01048	VV0079	12539	11316	MALIC ENZYME (EC 1.1.1.39)
579	580	F RXA01048	GR00296	3	290	MALIC ENZYME (EC 1.1.1.39)
581	582	F RXA00290	GR00046	4693	5655	MALIC ENZYME (EC 1.1.1.39)
583	584	RXN03101	VV0066	2	583	DIHYDROLIPOAMIDE SUCCINYLTRANSFERASE COMPONENT (E2) OF 2-OXOGLUTARATE DEHYDROGENASE COMPLEX (EC 2.3.1.61)
585	586	RXN02046	VV0025	15056	14640	DIHYDROLIPOAMIDE SUCCINYLTRANSFERASE COMPONENT OF 2-OXOGLUTARATE DEHYDROGENASE COMPLEX (EC 2.3.1.61)
587	588	RXN00389	VV0025	11481	9922	oxoglutarate semialdehyde dehydrogenase (EC 1.2.1.-)

Glyoxylate bypass

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
589	590	RXN02399	VV0176	19708	18365	ISOCITRATE LYASE (EC 4.1.3.1)
591	592	F RXA02399	GR00699	478	1773	ISOCITRATE LYASE (EC 4.1.3.1)
593	594	RXN02404	VV0176	20259	22475	MALATE SYNTHASE (EC 4.1.3.2)
595	596	F RXA02404	GR00700	3798	1663	MALATE SYNTHASE (EC 4.1.3.2)
597	598	RXA01089	GR00304	3209	3958	GLYOXYLATE-INDUCED PROTEIN
599	600	RXA01886	GR00539	3203	2430	GLYOXYLATE-INDUCED PROTEIN

Methylcitrate-pathway

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
601	602	RXN03117	VV0092	3087	1576	2-methylisocitrate synthase (EC 5.3.3.-)
603	604	F RXA00406	GR00090	978	4	2-methylisocitrate synthase (EC 5.3.3.-)
605	606	F RXA00514	GR00130	1983	1576	2-methylisocitrate synthase (EC 5.3.3.-)
607	608	RXA00512	GR00130	621	4	2-methylcitrate synthase (EC 4.1.3.31)
609	610	RXA00518	GR00131	3069	2773	2-methylcitrate synthase (EC 4.1.3.31)
611	612	RXA01077	GR00300	4647	6017	2-methylisocitrate synthase (EC 5.3.3.-)
613	614	RXN03144	VV0141	2	901	2-methylisocitrate synthase (EC 5.3.3.-)
615	616	F RXA02322	GR00668	415	5	2-methylisocitrate synthase (EC 5.3.3.-)
617	618	RXA02329	GR00669	607	5	2-methylisocitrate synthase (EC 5.3.3.-)
619	620	RXA02332	GR00671	1906	764	2-methylcitrate synthase (EC 4.1.3.31)
621	622	RXN02333	VV0141	901	1815	methylisocitrate lyase (EC 4.1.3.30)
623	624	F RXA02333	GR00671	2120	1902	methylisocitrate lyase (EC 4.1.3.30)
625	626	RXA00030	GR00003	9590	9979	LACTOYLGLUTATHIONE LYASE (EC 4.4.1.5)

Methyl-Malonyl-CoA-Mutases

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
627	628	RXN00148	VV0167	9849	12059	METHYLMALONYL-COA MUTASE ALPHA-SUBUNIT (EC 5.4.99.2)
629	630	F RXA00148	GR00023	2002	5	METHYLMALONYL-COA MUTASE ALPHA-SUBUNIT (EC 5.4.99.2)
631	632	RXA00149	GR00023	3856	2009	METHYLMALONYL-COA MUTASE BETA-SUBUNIT (EC 5.4.99.2)

Others

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
633	634	RXN00317	VV0197	26879	27532	PHOSPHOGLYCOLATE PHOSPHATASE (EC 3.1.3.18)
635	636	F RXA00317	GR00055	344	6	PHOSPHOGLYCOLATE PHOSPHATASE (EC 3.1.3.18)
637	638	RXA02196	GR00645	3956	3264	PHOSPHOGLYCOLATE PHOSPHATASE (EC 3.1.3.18)
639	640	RXN02461	VV0124	14236	14643	PHOSPHOGLYCOLATE PHOSPHATASE (EC 3.1.3.18)

Redox Chain

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
641	642	RXN01744	VV0174	2350	812	CYTOCHROME D UBIQUINOL OXIDASE SUBUNIT I (EC 1.10.3.-)
643	644	F RXA00055	GR00008	11753	11890	CYTOCHROME D UBIQUINOL OXIDASE SUBUNIT I (EC 1.10.3.-)
645	646	F RXA01744	GR00494	2113	812	CYTOCHROME D UBIQUINOL OXIDASE SUBUNIT I (EC 1.10.3.-)
647	648	RXA00379	GR00082	212	6	CYTOCHROME C-TYPE BIOGENESIS PROTEIN CCDA
649	650	RXA00385	GR00083	773	435	CYTOCHROME C-TYPE BIOGENESIS PROTEIN CCDA
651	652	RXA01743	GR00494	806	6	CYTOCHROME D UBIQUINOL OXIDASE SUBUNIT II (EC 1.10.3.-)
653	654	RXN02480	VV0084	31222	29567	CYTOCHROME C OXIDASE POLYPEPTIDE I (EC 1.9.3.1)
655	656	F RXA01919	GR00550	288	4	CYTOCHROME C OXIDASE SUBUNIT I (EC 1.9.3.1)
657	658	F RXA02480	GR00717	1449	601	CYTOCHROME C OXIDASE POLYPEPTIDE I (EC 1.9.3.1)
659	660	F RXA02481	GR00717	1945	1334	CYTOCHROME C OXIDASE POLYPEPTIDE I (EC 1.9.3.1)
661	662	RXA02140	GR00639	7339	8415	CYTOCHROME C OXIDASE POLYPEPTIDE II (EC 1.9.3.1)
663	664	RXA02142	GR00639	9413	10063	CYTOCHROME C OXIDASE POLYPEPTIDE I (EC 1.9.3.1)
665	666	RXA02144	GR00639	11025	12248	RIESKE IRON-SULFUR PROTEIN
667	668	RXA02740	GR00763	7613	8542	PROBABLE CYTOCHROME C OXIDASE ASSEMBLY FACTOR
669	670	RXA02743	GR00763	13534	12497	CYTOCHROME AA3 CONTROLLING PROTEIN
671	672	RXA01227	GR00355	1199	1519	FERREDOXIN
673	674	RXA01865	GR00532	436	122	FERREDOXIN
675	676	RXA00680	GR00179	2632	2315	FERREDOXIN VI
677	678	RXA00679	GR00179	2302	1037	FERREDOXIN--NAD(+) REDUCTASE (EC 1.18.1.3)
679	680	RXA00224	GR00032	24965	24015	ELECTRON TRANSFER FLAVOPROTEIN ALPHA-SUBUNIT
681	682	RXA00225	GR00032	25783	24998	ELECTRON TRANSFER FLAVOPROTEIN BETA-SUBUNIT
683	684	RXN00606	VV0192	11299	9026	NADH DEHYDROGENASE I CHAIN L (EC 1.6.5.3)
685	686	F RXA00606	GR00160	121	1869	NADH DEHYDROGENASE I CHAIN L (EC 1.6.5.3)
687	688	RXN00595	VV0192	8642	7113	NADH DEHYDROGENASE I CHAIN M (EC 1.6.5.3)
689	690	F RXA00608	GR00160	2253	3017	NADH DEHYDROGENASE I CHAIN M (EC 1.6.5.3)
691	692	RXA00913	GR00249	3	2120	NADH DEHYDROGENASE I CHAIN L (EC 1.6.5.3)
693	694	RXA00909	GR00247	2552	3406	NADH DEHYDROGENASE I CHAIN L (EC 1.6.5.3)
695	696	RXA00700	GR00182	846	43	NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 2
697	698	RXN00483	VV0086	44824	46287	NADH-UBIQUINONE OXIDOREDUCTASE 39 KD SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3)
699	700	F RXA00483	GR00119	19106	20569	NADH-UBIQUINONE OXIDOREDUCTASE 39 KD SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3)
701	702	RXA01534	GR00427	1035	547	NADH-DEPENDENT FMN OXYDOREDUCTASE

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
703	704	RXA00288	GR00046	2646	1636	QUINONE OXIDOREDUCTASE (EC 1.6.5.5)
705	706	RXA02741	GR00763	9585	8620	QUINONE OXIDOREDUCTASE (EC 1.6.5.5)
707	708	RXN02560	VV0101	9922	10788	NADPH-FLAVIN OXIDOREDUCTASE (EC 1.6.99.-)
709	710	F RXA02560	GR00731	6339	7160	NADPH-FLAVIN OXIDOREDUCTASE (EC 1.6.99.-)
711	712	RXA01311	GR00380	1611	865	SUCCINATE DEHYDROGENASE IRON-SULFUR PROTEIN (EC 1.3.99.1)
713	714	RXN03014	VV0058	1273	368	NADH DEHYDROGENASE I CHAIN M (EC 1.6.5.3)
715	716	F RXA00910	GR00248	3	1259	Hydrogenase subunits
717	718	RXN01895	VV0117	955	5	NADH DEHYDROGENASE (EC 1.6.99.3)
719	720	F RXA01895	GR00543	2	817	DEHYDROGENASE
721	722	RXA00703	GR00183	2556	271	FORMATE DEHYDROGENASE ALPHA CHAIN (EC 1.2.1.2)
723	724	RXN00705	VV0005	6111	5197	FDHD PROTEIN
725	726	F RXA00705	GR00184	1291	407	FDHD PROTEIN
727	728	RXN00388	VV0025	2081	3091	CYTOCHROME C BIOGENESIS PROTEIN CCSA
729	730	F RXA00388	GR00085	969	667	essential protein similar to cytochrome c
731	732	F RXA00386	GR00084	514	5	RESC PROTEIN, essential protein similar to cytochrome c biogenesis protein
733	734	RXA00945	GR00259	1876	2847	putative cytochrome oxidase
735	736	RXN02556	VV0101	5602	6759	FLAVOHEMOPROTEIN / DIHYDROPTERIDINE REDUCTASE (EC 1.6.99.7)
737	738	F RXA02556	GR00731	2019	3176	FLAVOHEMOPROTEIN
739	740	RXA01392	GR00408	2297	3373	GLUTATHIONE S-TRANSFERASE (EC 2.5.1.18)
741	742	RXA00800	GR00214	2031	3134	GLUTATHIONE-DEPENDENT FORMALDEHYDE DEHYDROGENASE (EC 1.2.1.1)
743	744	RXA02143	GR00639	10138	11025	QCRC PROTEIN, menaquinol:cytochrome c oxidoreductase
745	746	RXN03096	VV0058	405	4	NADH DEHYDROGENASE I CHAIN M (EC 1.6.5.3)
747	748	RXN02036	VV0176	32683	33063	NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 4 (EC 1.6.5.3)
749	750	RXN02765	VV0317	3552	2794	Hypothetical Oxidorductase
751	752	RXN02206	VV0302	1784	849	Hypothetical Oxidoreductase
753	754	RXN02554	VV0101	4633	4010	Hypothetical Oxidoreductase (EC 1.1.1.-)

ATP-Synthase

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
755	756	RXN01204	VV0121	1270	461	ATP SYNTHASE A CHAIN (EC 3.6.1.34)
757	758	F RXA01204	GR00345	394	1155	ATP SYNTHASE A CHAIN (EC 3.6.1.34)
759	760	RXA01201	GR00344	675	2315	ATP SYNTHASE ALPHA CHAIN (EC 3.6.1.34)
761	762	RXN01193	VV0175	5280	3832	ATP SYNTHASE BETA CHAIN (EC 3.6.1.34)
763	764	F RXA01193	GR00343	15	755	ATP SYNTHASE BETA CHAIN (EC 3.6.1.34)
765	766	F RXA01203	GR00344	3355	3993	ATP SYNTHASE BETA CHAIN (EC 3.6.1.34)
767	768	RXN02821	VV0121	324	85	ATP SYNTHASE C CHAIN (EC 3.6.1.34)
769	770	F RXA02821	GR00802	139	318	ATP SYNTHASE C CHAIN (EC 3.6.1.34)
771	772	RXA01200	GR00344	2	610	ATP SYNTHASE DELTA CHAIN (EC 3.6.1.34)
773	774	RXA01194	GR00343	770	1141	ATP SYNTHASE EPSILON CHAIN (EC 3.6.1.34)

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
775	776	RXA01202	GR00344	2375	3349	ATP SYNTHASE GAMMA CHAIN (EC 3.6.1.34)
777	778	RXN02434	VV0090	4923	3274	ATP-BINDING PROTEIN

Cytochrome metabolism

Nucleic Acid SEQ ID NO	Amino Acid SEQ ID NO	Identification Code	Contig.	NT Start	NT Stop	Function
779	780	RXN00684	VV0005	29864	28581	CYTOCHROME P450 116 (EC 1.14.-.-)
781	782	RXN00387	VV0025	1150	2004	Hypothetical Cytochrome c Biogenesis Protein

TABLE 2: GENES IDENTIFIED FROM GENBANK

GenBank™ Accession No.	Gene Name	Gene Function	Reference
A09073	ppg	Phosphoenol pyruvate carboxylase	Bachmann, B. et al. "DNA fragment coding for phosphoenolpyruvat corboxylase, recombinant DNA carrying said fragment, strains carrying the recombinant DNA and method for producing L-aminino acids using said strains," Patent: EP 0358940-A 3 03/21/90
A45579, A45581, A45583, A45585 A45587		Threonine dehydratase	Moeckel, B. et al. "Production of L-isoleucine by means of recombinant micro-organisms with deregulated threonine dehydratase," Patent: WO 9519442-A 5 07/20/95
AB003132	murC; ftsQ; ftsZ		Kobayashi, M. et al. "Cloning, sequencing, and characterization of the ftsZ gene from coryneform bacteria," *Biochem. Biophys. Res. Commun.*, 236(2):383-388 (1997)
AB015023	murC; ftsQ		Wachi, M. et al. "A murC gene from Coryneform bacteria," *Appl. Microbiol. Biotechnol.*, 51(2):223-228 (1999)
AB018530	dtsR		Kimura, E. et al. "Molecular cloning of a novel gene, dtsR, which rescues the detergent sensitivity of a mutant derived from *Brevibacterium lactofermentum*," *Biosci. Biotechnol. Biochem.*, 60(10):1565-1570 (1996)
AB018531	dtsR1; dtsR2		
AB020624	murI	D-glutamate racemase	
AB023377	tkt	transketolase	
AB024708	gltB; gltD	Glutamine 2-oxoglutarate aminotransferase large and small subunits	
AB025424	acn	aconitase	
AB027714	rep	Replication protein	
AB027715	rep; aad	Replication protein; aminoglycoside adenyltransferase	
AF005242	argC	N-acetylglutamate-5-semialdehyde dehydrogenase	
AF005635	glnA	Glutamine synthetase	
AF030405	hisF	cyclase	
AF030520	argG	Argininosuccinate synthetase	
AF031518	argF	Ornithine carbamolytransferase	
AF036932	aroD	3-dehydroquinate dehydratase	

GenBank™ Accession No.	Gene Name	Gene Function	Reference
AF038548	pyc	Pyruvate carboxylase	
AF038651	dciAE; apt; rel	Dipeptide-binding protein; adenine phosphoribosyltransferase; GTP pyrophosphokinase	Wehmeier, L. et al. "The role of the Corynebacterium glutamicum rel gene in (p)ppGpp metabolism," *Microbiology,* 144:1853-1862 (1998)
AF041436	argR	Arginine repressor	
AF045998	impA	Inositol monophosphate phosphatase	
AF048764	argH	Argininosuccinate lyase	
AF049897	argC; argJ; argB; argD; argF; argR; argG; argH	N-acetylglutamylphosphate reductase; ornithine acetyltransferase; N-acetylglutamate kinase; acetylornithine transminase; ornithine carbamoyltransferase; arginine repressor; argininosuccinate synthase; argininosuccinate lyase	
AF050109	inhA	Enoyl-acyl carrier protein reductase	
AF050166	hisG	ATP phosphoribosyltransferase	
AF051846	hisA	Phosphoribosylformimino-5-amino-1-phosphoribosyl-4-imidazolecarboxamide isomerase	
AF052652	metA	Homoserine O-acetyltransferase	Park, S. et al. "Isolation and analysis of metA, a methionine biosynthetic gene encoding homoserine acetyltransferase in Corynebacterium glutamicum," *Mol. Cells.,* 8(3):286-294 (1998)
AF053071	aroB	Dehydroquinate synthetase	
AF060558	hisH	Glutamine amidotransferase	
AF086704	hisE	Phosphoribosyl-ATP-pyrophosphohydrolase	
AF114233	aroA	5-enolpyruvylshikimate 3-phosphate synthase	
AF116184	panD	L-aspartate-alpha-decarboxylase precursor	Dusch, N. et al. "Expression of the Corynebacterium glutamicum panD gene encoding L-aspartate-alpha-decarboxylase leads to pantothenate overproduction in Escherichia coli," *Appl. Environ. Microbiol.,* 65(4)1530-1539 (1999)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
AF124518	aroD; aroE	3-dehydroquinase; shikimate dehydrogenase	
AF124600	aroC; aroK; aroB; pepQ	Chorismate synthase; shikimate kinase; 3-dehydroquinate synthase; putative cytoplasmic peptidase	
AF145897	inhA		
AF145898	inhA		
AJ001436	ectP	Transport of ectoine, glycine betaine, proline	Peter, H. et al. "Corynebacterium glutamicum is equipped with four secondary carriers for compatible solutes: Identification, sequencing, and characterization of the proline/ectoine uptake system, ProP, and the ectoine/proline/glycine betaine carrier, EctP," *J. Bacteriol.*, 180(22):6005-6012 (1998)
AJ004934	dapD	Tetrahydrodipicolinate succinylase (incomplete[i])	Wehrmann, A. et al. "Different modes of diaminopimelate synthesis and their role in cell wall integrity: A study with Corynebacterium glutamicum," *J. Bacteriol.*, 180(12):3159-3165 (1998)
AJ007732	ppc; secG; amt; ocd; soxA	Phosphoenolpyruvate-carboxylase; ?; high affinity ammonium uptake protein; putative ornithine-cyclodecarboxylase; sarcosine oxidase	
AJ010319	ftsY, glnB, glnD; srp; amtP	Involved in cell division; PII protein; uridylyltransferase (uridylyl-removing enzmye); signal recognition particle; low affinity ammonium uptake protein	Jakoby, M. et al. "Nitrogen regulation in Corynebacterium glutamicum; Isolation of genes involved in biochemical characterization of corresponding proteins," *FEMS Microbiol.*, 173(2):303-310 (1999)
AJ132968	cat	Chloramphenicol aceteyl transferase	
AJ224946	mqo	L-malate: quinone oxidoreductase	Molenaar, D. et al. "Biochemical and genetic characterization of the membrane-associated malate dehydrogenase (acceptor) from Corynebacterium glutamicum," *Eur. J. Biochem.*, 254(2):395-403 (1998)
AJ238250	ndh	NADH dehydrogenase	
AJ238703	porA	Porin	Lichtinger, T. et al. "Biochemical and biophysical characterization of the cell wall porin of Corynebacterium glutamicum: The channel is formed by a low molecular mass polypeptide," *Biochemistry*, 37(43):15024-15032 (1998)
D17429		Transposable element IS31831	Vertes, A.A. et al. "Isolation and characterization of IS31831, a transposable element from Corynebacterium glutamicum," *Mol. Microbiol.*, 11(4):739-746 (1994)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
D84102	odhA	2-oxoglutarate dehydrogenase	Usuda, Y. et al. "Molecular cloning of the Corynebacterium glutamicum (Brevibacterium lactofermentum AJ12036) odhA gene encoding a novel type of 2-oxoglutarate dehydrogenase," *Microbiology,* 142:3347-3354 (1996)
E01358	hdh; hk	Homoserine dehydrogenase; homoserine kinase	Katsumata, R. et al. "Production of L-thereonine and L-isoleucine," Patent: JP 1987232392-A 1 10/12/87
E01359		Upstream of the start codon of homoserine kinase gene	Katsumata, R. et al. "Production of L-thereonine and L-isoleucine," Patent: JP 1987232392-A 2 10/12/87
E01375		Tryptophan operon	
E01376	trpL; trpE	Leader peptide; anthranilate synthase	Matsui, K. et al. "Tryptophan operon, peptide and protein coded thereby, utilization of tryptophan operon gene expression and production of tryptophan," Patent: JP 1987244382-A 1 10/24/87
E01377		Promoter and operator regions of tryptophan operon	Matsui, K. et al. "Tryptophan operon, peptide and protein coded thereby, utilization of tryptophan operon gene expression and production of tryptophan," Patent: JP 1987244382-A 1 10/24/87
E03937		Biotin-synthase	Hatakeyama, K. et al. "DNA fragment containing gene capable of coding biotin synthetase and its utilization," Patent: JP 1992278088-A 1 10/02/92
E04040		Diamino pelargonic acid aminotransferase	Kohama, K. et al. "Gene coding diaminopelargonic acid aminotransferase and desthiobiotin synthetase and its utilization," Patent: JP 1992330284-A 1 11/18/92
E04041		Desthiobiotinsynthetase	Kohama, K. et al. "Gene coding diaminopelargonic acid aminotransferase and desthiobiotin synthetase and its utilization," Patent: JP 1992330284-A 1 11/18/92
E04307		Flavum aspartase	Kurusu, Y. et al. "Gene DNA coding aspartase and utilization thereof," Patent: JP 1993030977-A 1 02/09/93
E04376		Isocitric acid lyase	Katsumata, R. et al. "Gene manifestation controlling DNA," Patent: JP 1993056782-A 3 03/09/93
E04377		Isocitric acid lyase N-terminal fragment	Katsumata, R. et al. "Gene manifestation controlling DNA," Patent: JP 1993056782-A 3 03/09/93
E04484		Prephenate dehydratase	Sotouchi, N. et al. "Production of L-phenylalanine by fermentation," Patent: JP 1993076352-A 2 03/30/93
E05108		Aspartokinase	Fugono, N. et al. "Gene DNA coding Aspartokinase and its use," Patent: JP 1993184366-A 1 07/27/93
E05112		Dihydro-dipichorinate synthetase	Hatakeyama, K. et al. "Gene DNA coding dihydrodipicolinic acid synthetase and its use," Patent: JP 1993184371-A 1 07/27/93

GenBank™ Accession No.	Gene Name	Gene Function	Reference
E05776		Diaminopimelic acid dehydrogenase	Kobayashi, M. et al. "Gene DNA coding Diaminopimelic acid dehydrogenase and its use," Patent: JP 1993284970-A 1 11/02/93
E05779		Threonine synthase	Kohama, K. et al. "Gene DNA coding threonine synthase and its use," Patent: JP 1993284972-A 1 11/02/93
E06110		Prephenate dehydratase	Kikuchi, T. et al. "Production of L-phenylalanine by fermentation method," Patent: JP 1993344881-A 1 12/27/93
E06111		Mutated Prephenate dehydratase	Kikuchi, T. et al. "Production of L-phenylalanine by fermentation method," Patent: JP 1993344881-A 1 12/27/93
E06146		Acetohydroxy acid synthetase	Inui, M. et al. "Gene capable of coding Acetohydroxy acid synthetase and its use," Patent: JP 1993344893-A 1 12/27/93
E06825		Aspartokinase	Sugimoto, M. et al. "Mutant aspartokinase gene," patent: JP 1994062866-A 1 03/08/94
E06826		Mutated aspartokinase alpha subunit	Sugimoto, M. et al. "Mutant aspartokinase gene," patent: JP 1994062866-A 1 03/08/94
E06827		Mutated aspartokinase alpha subunit	Sugimoto, M. et al. "Mutant aspartokinase gene," patent: JP 1994062866-A 1 03/08/94
E07701	secY		Honno, N. et al. "Gene DNA participating in integration of membraneous protein to membrane," Patent: JP 1994169780-A 1 06/21/94
E08177		Aspartokinase	Sato, Y. et al. "Genetic DNA capable of coding Aspartokinase released from feedback inhibition and its utilization," Patent: JP 1994261766-A 1 09/20/94
E08178, E08179, E08180, E08181, E08182		Feedback inhibition-released Aspartokinase	Sato, Y. et al. "Genetic DNA capable of coding Aspartokinase released from feedback inhibition and its utilization," Patent: JP 1994261766-A 1 09/20/94
E08232		Acetohydroxy-acid isomeroreductase	Inui, M. et al. "Gene DNA coding acetohydroxy acid isomeroreductase," Patent: JP 1994277067-A 1 10/04/94
E08234	secE		Asai, Y. et al. "Gene DNA coding for translocation machinery of protein," Patent: JP 1994277073-A 1 10/04/94
E08643		FT aminotransferase and desthiobiotin synthetase promoter region	Hatakeyama, K. et al. "DNA fragment having promoter function in coryneform bacterium," Patent: JP 1995031476-A 1 02/03/95
E08646		Biotin synthetase	Hatakeyama, K. et al. "DNA fragment having promoter function in coryneform bacterium," Patent: JP 1995031476-A 1 02/03/95

GenBank™ Accession No.	Gene Name	Gene Function	Reference
E08649		Aspartase	Kohama, K. et al "DNA fragment having promoter function in coryneform bacterium," Patent: JP 1995031478-A 1 02/03/95
E08900		Dihydrodipicolinate reductase	Madori, M. et al. "DNA fragment containing gene coding Dihydrodipicolinate acid reductase and utilization thereof," Patent: JP 1995075578-A 1 03/20/95
E08901		Diaminopimelic acid decarboxylase	Madori, M. et al. "DNA fragment containing gene coding Diaminopimelic acid decarboxylase and utilization thereof," Patent: JP 1995075579-A 1 03/20/95
E12594		Serine hydroxymethyltransferase	Hatakeyama, K. et al. "Production of L-trypophan," Patent: JP 1997028391-A 1 02/04/97
E12760, E12759, E12758		transposase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent: JP 1997070291-A 03/18/97
E12764		Arginyl-tRNA synthetase; diaminopimelic acid decarboxylase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent: JP 1997070291-A 03/18/97
E12767		Dihydrodipicolinic acid synthetase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent: JP 1997070291-A 03/18/97
E12770		aspartokinase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent: JP 1997070291-A 03/18/97
E12773		Dihydrodipicolinic acid reductase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent: JP 1997070291-A 03/18/97
E13655		Glucose-6-phosphate dehydrogenase	Hatakeyama, K. et al. "Glucose-6-phosphate dehydrogenase and DNA capable of coding the same," Patent: JP 1997224661-A 1 09/02/97
L01508	IlvA	Threonine dehydratase	Moeckel, B. et al. "Functional and structural analysis of the threonine dehydratase of Corynebacterium glutamicum," *J. Bacteriol.*, 174:8065-8072 (1992)
L07603	EC 4.2.1.15	3-deoxy-D-arabinoheptulosonate-7-phosphate synthase	Chen, C. et al. "The cloning and nucleotide sequence of Corynebacterium glutamicum 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase gene," *FEMS Microbiol. Lett.*, 107:223-230 (1993)
L09232	IlvB; ilvN; ilvC	Acetohydroxy acid synthase large subunit; Acetohydroxy acid synthase small subunit; Acetohydroxy acid isomeroreductase	Keilhauer, C. et al. "Isoleucine synthesis in Corynebacterium glutamicum: molecular analysis of the ilvB-ilvN-ilvC operon," *J. Bacteriol.*, 175(17):5595-5603 (1993)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
L18874	PtsM	Phosphoenolpyruvate sugar phosphotransferase	Fouet, A et al. "Bacillus subtilis sucrose-specific enzyme II of the phosphotransferase system: expression in Escherichia coli and homology to enzymes II from enteric bacteria," *PNAS USA*, 84(24):8773-8777 (1987); Lee, J.K. et al. "Nucleotide sequence of the gene encoding the Corynebacterium glutamicum mannose enzyme II and analyses of the deduced protein sequence," *FEMS Microbiol. Lett.*, 119(1-2):137-145 (1994)
L27123	aceB	Malate synthase	Lee, H-S. et al. "Molecular characterization of aceB, a gene encoding malate synthase in Corynebacterium glutamicum," *J. Microbiol. Biotechnol.*, 4(4):256-263 (1994)
L27126		Pyruvate kinase	Jetten, M. S. et al. "Structural and functional analysis of pyruvate kinase from Corynebacterium glutamicum," *Appl. Environ. Microbiol.*, 60(7):2501-2507 (1994)
L28760	aceA	Isocitrate lyase	
L35906	dtxr	Diphtheria toxin repressor	Oguiza, J.A. et al. "Molecular cloning, DNA sequence analysis, and characterization of the Corynebacterium diphtheriae dtxR from Brevibacterium lactofermentum," *J. Bacteriol.*, 177(2):465-467 (1995)
M13774		Prephenate dehydratase	Follettie, M.T. et al. "Molecular cloning and nucleotide sequence of the Corynebacterium glutamicum pheA gene," *J. Bacteriol.*, 167:695-702 (1986)
M16175	5S rRNA		Park, Y-H. et al. "Phylogenetic analysis of the coryneform bacteria by 56 rRNA sequences," *J. Bacteriol.*, 169:1801-1806 (1987)
M16663	trpE	Anthranilate synthase, 5' end	Sano, K. et al. "Structure and function of the trp operon control regions of Brevibacterium lactofermentum, a glutamic-acid-producing bacterium," *Gene*, 52:191-200 (1987)
M16664	trpA	Tryptophan synthase, 3'end	Sano, K. et al. "Structure and function of the trp operon control regions of Brevibacterium lactofermentum, a glutamic-acid-producing bacterium," *Gene*, 52:191-200 (1987)
M25819		Phosphoenolpyruvate carboxylase	O'Regan, M. et al. "Cloning and nucleotide sequence of the Phosphoenolpyruvate carboxylase-coding gene of Corynebacterium glutamicum ATCC13032," *Gene*, 77(2):237-251 (1989)
M85106		23S rRNA gene insertion sequence	Roller, C. et al. "Gram-positive bacteria with a high DNA G+C content are characterized by a common insertion within their 23S rRNA genes," *J. Gen. Microbiol.*, 138:1167-1175 (1992)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
M85107, M85108		23S rRNA gene insertion sequence	Roller, C. et al. "Gram-positive bacteria with a high DNA G+C content are characterized by a common insertion within their 23S rRNA genes," *J. Gen. Microbiol.*, 138:1167-1175 (1992)
M89931	aecD; brnQ; yhbw	Beta C-S lyase; branched-chain amino acid uptake carrier; hypothetical protein yhbw	Rossol, I. et al. "The Corynebacterium glutamicum aecD gene encodes a C-S lyase with alpha, beta-elimination activity that degrades aminoethylcysteine," *J. Bacteriol.*, 174(9):2968-2977 (1992); Tauch, A. et al. "Isoleucine uptake in Corynebacterium glutamicum ATCC 13032 is directed by the brnQ gene product," *Arch. Microbiol.*, 169(4):303-312 (1998)
S59299	trp	Leader gene (promoter)	Herry, D.M. et al. "Cloning of the trp gene cluster from a tryptophan-hyperproducing strain of Corynebacterium glutamicum: identification of a mutation in the trp leader sequence," *Appl. Environ. Microbiol.*, 59(3):791-799 (1993)
U11545	trpD	Anthranilate phosphoribosyltransferase	O'Gara, J.P. and Dunican, L.K. (1994) Complete nucleotide sequence of the Corynebacterium glutamicum ATCC 21850 tpD gene." Thesis, Microbiology Department, University College Galway, Ireland.
U13922	cglIM; cglIR; clgIIR	Putative type II 5-cytosoine methyltransferase; putative type II restriction endonuclease; putative type I or type III restriction endonuclease	Schafer, A. et al. "Cloning and characterization of a DNA region encoding a stress-sensitive restriction system from Corynebacterium glutamicum ATCC 13032 and analysis of its role in intergeneric conjugation with Escherichia coli," *J. Bacteriol.*, 176(23):7309-7319 (1994); Schafer, A. et al. "The Corynebacterium glutamicum cglIM gene encoding a 5-cytosine in an McrBC-deficient Escherichia coli strain," *Gene*, 203(2):95-101 (1997)
U14965	recA		
U31224	ppx		Ankri, S. et al. "Mutations in the Corynebacterium glutamicumproline biosynthetic pathway: A natural bypass of the proA step," *J. Bacteriol.*, 178(15):4412-4419 (1996)
U31225	proC	L-proline: NADP+ 5-oxidoreductase	Ankri, S. et al. "Mutations in the Corynebacterium glutamicumproline biosynthetic pathway: A natural bypass of the proA step," *J. Bacteriol.*, 178(15):4412-4419 (1996)
U31230	obg; proB; unkdh	?;gamma glutamyl kinase;similar to D-isomer specific 2-hydroxyacid dehydrogenases	Ankri, S. et al. "Mutations in the Corynebacterium glutamicumproline biosynthetic pathway: A natural bypass of the proA step," *J. Bacteriol.*, 178(15):4412-4419 (1996)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
U31281	bioB	Biotin synthase	Serebriiskii, I.G., "Two new members of the bio B superfamily: Cloning, sequencing and expression of bio B genes of Methylobacillus flagellatum and Corynebacterium glutamicum," *Gene,* 175:15-22 (1996)
U35023	thtR; accBC	Thiosulfate sulfurtransferase; acyl CoA carboxylase	Jager, W. et al. "A Corynebacterium glutamicum gene encoding a two-domain protein similar to biotin carboxylases and biotin-carboxyl-carrier proteins," *Arch. Microbiol.,* 166(2);76-82 (1996)
U43535	cmr	Multidrug resistance protein	Jager, W. et al. "A Corynebacterium glutamicum gene conferring multidrug resistance in the heterologous host Escherichia coli," *J. Bacteriol.,* 179(7):2449-2451 (1997)
U43536	clpB	Heat shock ATP-binding protein	
U53587	aphA-3	3'5''-aminoglycoside phosphotransferase	
U89648		Corynebacterium glutamicum unidentified sequence involved in histidine biosynthesis, partial sequence	
X04960	trpA; trpB; trpC; trpD; trpE; trpG; trpL	Tryptophan operon	Matsui, K. et al. "Complete nucleotide and deduced amino acid sequences of the Brevibacterium lactofermentum tryptophan operon," *Nucleic Acids Res.,* 14(24):10113-10114 (1986)
X07563	lys A	DAP decarboxylase (meso-diaminopimelate decarboxylase, EC 4.1.1.20)	Yeh, P. et al. "Nucleic sequence of the lysA gene of Corynebacterium glutamicum and possible mechanisms for modulation of its expression," *Mol. Gen. Genet.,* 212(1):112-119 (1988)
X14234	EC 4.1.1.31	Phosphoenolpyruvate carboxylase	Eikmanns, B.J. et al. "The Phosphoenolpyruvate carboxylase gene of Corynebacterium glutamicum: Molecular cloning, nucleotide sequence, and expression," *Mol. Gen. Genet.,* 218(2):330-339 (1989); Lepiniec, L. et al. "Sorghum Phosphoenolpyruvate carboxylase gene family: structure, function and molecular evolution," *Plant. Mol. Biol.,* 21 (3):487-502 (1993)
X17313	fda	Fructose-bisphosphate aldolase	Von der Osten, C.H. et al. "Molecular cloning, nucleotide sequence and fine-structural analysis of the Corynebacterium glutamicum fda gene: structural comparison of C. glutamicum fructose-1, 6-biphosphate aldolase to class I and class II aldolases," *Mol. Microbiol.,*
X53993	dapA	L-2, 3-dihydrodipicolinate synthetase (EC 4.2.1.52)	Bonnassie, S. et al. "Nucleic sequence of the dapA gene from Corynebacterium glutamicum," *Nucleic Acids Res.,* 18(21):6421 (1990)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
X54223		AttB-related site	Cianciotto, N. et al. "DNA sequence homology between att B-related sites of Corynebacterium diphtheriae, Corynebacterium ulcerans, Corynebacterium glutamicum , and the attP site of lambdacorynephage," *FEMS. Microbiol, Lett.*, 66:299-302 (1990)
X54740	argS; lysA	Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	Marcel, T. et al. "Nucleotide sequence and organization of the upstream region of the Corynebacterium glutamicum lysA gene," *Mol. Microbiol.*, 4(11):1819-1830 (1990)
X55994	trpL; trpE	Putative leader peptide; anthranilate synthase component 1	Heery, D.M. et al. "Nucleotide sequence of the Corynebacterium glutamicum trpE gene," *Nucleic Acids Res.*, 18(23):7138 (1990)
X56037	thrC	Threonine synthase	Han, K.S. et al. "The molecular structure of the Corynebacterium glutamicum threonine synthase gene," *Mol. Microbiol.*, 4(10):1693-1702 (1990)
X56075	attB-related site	Attachment site	Cianciotto, N. et al. "DNA sequence homology between att B-related sites of Corynebacterium diphtheriae, Corynebacterium ulcerans, Corynebacterium glutamicum , and the attP site of lambdacorynephage," *FEMS. Microbiol, Lett.*, 66:299-302 (1990)
X57226	lysC-alpha; lysC-beta; asd	Aspartokinase-alpha subunit; Aspartokinase-beta subunit; aspartate beta semialdehyde dehydrogenase	Kalinowski, J. et al. "Genetic and biochemical analysis of the Aspartokinase from Corynebacterium glutamicum," *Mol. Microbiol.*, 5(5):1197-1204 (1991); Kalinowski, J. et al. "Aspartokinase genes lysC alpha and lysC beta overlap and are adjacent to the aspertate beta-semialdehyde dehydrogenase gene asd in Corynebacterium glutamicum," *Mol. Gen. Genet.*, 224(3):317-324 (1990)
X59403	gap;pgk; tpi	Glyceraldehyde-3-phosphate; phosphoglycerate kinase; triosephosphate isomerase	Eikmanns, B.J. "Identification, sequence analysis, and expression of a Corynebacterium glutamicum gene cluster encoding the three glycolytic enzymes glyceraldehyde-3-phosphate dehydrogenase, 3-phosphoglycerate kinase, and triosephosphate isomeras," *J. Bacteriol.*, 174(19):6076-6086 (1992)
X59404	gdh	Glutamate dehydrogenase	Bormann, E.R. et al. "Molecular analysis of the Corynebacterium glutamicum gdh gene encoding glutamate dehydrogenase," *Mol. Microbiol.*, 6(3):317-326 (1992)
X60312	lysI	L-lysine permease	Seep-Feldhaus, A.H. et al. "Molecular analysis of the Corynebacterium glutamicum lysI gene involved in lysine uptake," *Mol. Microbiol.*, 5(12):2995-3005 (1991)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
X66078	cop1	Ps1 protein	Joliff, G. et al. "Cloning and nucleotide sequence of the csp1 gene encoding PS1, one of the two major secreted proteins of Corynebacterium glutamicum: The deduced N-terminal region of PS1 is similar to the Mycobacterium antigen 85 complex," *Mol. Microbiol.*, 6(16):2349-2362 (1992)
X66112	glt	Citrate synthase	Eikmanns, B.J. et al. "Cloning sequence, expression and transcriptional analysis of the Corynebacterium glutamicum gltA gene encoding citrate synthase," *Microbiol.*, 140:1817-1828 (1994)
X67737	dapB	Dihydrodipicolinate reductase	
X69103	csp2	Surface layer protein PS2	Peyret, J.L. et al. "Characterization of the cspB gene encoding PS2, an ordered surface-layer protein in Corynebacterium glutamicum," *Mol. Microbiol.*, 9(1):97-109 (1993)
X69104		IS3 related insertion element	Bonamy, C. et al. "Identification of IS1206, a Corynebacterium glutamicum IS3-related insertion sequence and phylogenetic analysis," *Mol. Microbiol.*, 14(3):571-581 (1994)
X70959	leuA	Isopropylmalate synthase	Patek, M. et al. "Leucine synthesis in Corynebacterium glutamicum: enzyme activities, structure of leuA, and effect of leuA inactivation on lysine synthesis," *Appl. Environ. Microbiol.*, 60(1):133-140 (1994)
X71489	icd	Isocitrate dehydrogenase (NADP+)	Eikmanns, B.J. et al. "Cloning sequence analysis, expression, and inactivation of the Corynebacterium glutamicum icd gene encoding isocitrate dehydrogenase and biochemical characterization of the enzyme," *J. Bacteriol.*, 177(3):774-782 (1995)
X72855	GDHA	Glutamate dehydrogenase (NADP+)	
X75083, X70584	mtrA	5-methyltryptophan resistance	Heery, D.M. et al. "A sequence from a tryptophan-hyperproducing strain of Corynebacterium glutamicum encoding resistance to 5-methyltryptophan," *Biochem. Biophys. Res. Commun.*, 201(3):1255-1262 (1994)
X75085	recA		Fitzpatrick, R. et al. "Construction and characterization of recA mutant strains of Corynebacterium glutamicum and Brevibacterium lactofermentum," *Appl. Microbiol. Biotechnol.*, 42(4):575-580 (1994)
X75504	aceA; thiX	Partial Isocitrate lyase; ?	Reinscheid, D.J. et al. "Characterization of the isocitrate lyase gene from Corynebacterium glutamicum and biochemical analysis of the enzyme," *J. Bacteriol.*, 176(12):3474-3483 (1994)
X76875		ATPase beta-subunit	Ludwig, W. et al. "Phylogenetic relationships of bacteria based on comparative sequence analysis of elongation factor Tu and ATP-synthase beta-subunit genes," *Antonie Van Leeuwenhoek*, 64:285-305 (1993)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
X77034	tuf	Elongation factor Tu	Ludwig, W. et al. "Phylogenetic relationships of bacteria based on comparative sequence analysis of elongation factor Tu and ATP-synthase beta-subunit genes," *Antonie Van Leeuwenhoek,* 64:285-305 (1993)
X77384	recA		Billman-Jacobe, H. "Nucleotide sequence of a recA gene from Corynebacterium glutamicum," *DNA Seq.,* 4(6):403-404 (1994)
X78491	aceB	Malate synthase	Reinscheid, D.J. et al. "Malate synthase from Corynebacterium glutamicum pta-ack operon encoding phosphotransacetylase: sequence analysis," *Microbiology,* 140:3099-3108 (1994)
X80629	16S rDNA	16S ribosomal RNA	Rainey, F.A. et al. "Phylogenetic analysis of the genera Rhodococcus and Norcardia and evidence for the evolutionary origin of the genus Norcardia from within the radiation of Rhodococcus species," *Microbiol.,* 141:523-528 (1995)
X81191	gluA; gluB; gluC; gluD	Glutamate uptake system	Kronemeyer, W. et al. "Structure of the gluABCD cluster encoding the glutamate uptake system of Corynebacterium glutamicum," *J. Bacteriol.,* 177(5):1152-1158 (1995)
X81379	dapE	Succinyldiaminopimelate desuccinylase	Wehrmann, A. et al. "Analysis of different DNA fragments of Corynebacterium glutamicum complementing dapE of Escherichia coli," *Microbiology,* 40:3349-56 (1994)
X82061	16S rDNA	16S ribosomal RNA	Ruimy, R. et al. "Phylogeny of the genus Corynebacterium deduced from analyses of small-subunit ribosomal DNA sequences," *Int. J. Syst. Bacteriol.,* 45(4):740-746 (1995)
X82928	asd; lysC	Aspartate-semialdehyde dehydrogenase; ?	Serebrijski, I. et al. "Multicopy suppression by asd gene and osmotic stress-dependent complementation by heterologous proA in proA mutants," *J. Bacteriol.,* 177(24):7255-7260 (1995)
X82929	proA	Gamma-glutamyl phosphate reductase	Serebrijski, I. et al. "Multicopy suppression by asd gene and osmotic stress-dependent complementation by heterologous proA in proA mutants," *J. Bacteriol.,* 177(24):7255-7260 (1995)
X84257	16S rDNA	16S ribosomal RNA	Pascual, C. et al. "Phylogenetic analysis of the genus Corynebacterium based on 16S rRNA gene sequences," *Int. J. Syst. Bacteriol.,* 45(4):724-728 (1995)
X85965	aroP; dapE	Aromatic amino acid permease; ?	Wehrmann, A. et al. "Functional analysis of sequences adjacent to dapE of Corynebacterium glutamicumproline reveals the presence of aroP, which encodes the aromatic amino acid transporter," *J. Bacteriol.,* 177(20):5991-5993 (1995)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
X86157	argB; argC; argD; argF; argJ	Acetylglutamate kinase; N-acetyl-gamma-glutamyl-phosphate reductase; acetylornithine aminotransferase; ornithine carbamoyltransferase; glutamate N-acetyltransferase	Sakanyan, V. et al. "Genes and enzymes of the acetyl cycle of arginine biosynthesis in Corynebacterium glutamicum: enzyme evolution in the early steps of the arginine pathway," *Microbiology,* 142:99-108 (1996)
X89084	pta; ackA	Phosphate acetyltransferase; acetate kinase	Reinscheid, D.J. et al. "Cloning, sequence analysis, expression and inactivation of the Corynebacterium glutamicum pta-ack operon encoding phosphotransacetylase and acetate kinase," *Microbiology,* 145:503-513 (1999)
X89850	attB	Attachment site	Le Marrec, C. et al. "Genetic characterization of site-specific integration functions of phi AAU2 infecting "Arthrobacter aureus C70," *J. Bacteriol.*, 178(7):1996-2004 (1996)
X90356		Promoter fragment F1	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90357		Promoter fragment F2	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90358		Promoter fragment F10	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90359		Promoter fragment F13	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90360		Promoter fragment F22	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90361		Promoter fragment F34	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90362		Promoter fragment F37	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
X90363		Promoter fragment F45	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90364		Promoter fragment F64	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90365		Promoter fragment F75	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90366		Promoter fragment PF101	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90367		Promoter fragment PF104	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X90368		Promoter fragment PF109	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," *Microbiology,* 142:1297-1309 (1996)
X93513	amt	Ammonium transport system	Siewe, R.M. et al. "Functional and genetic characterization of the (methyl) ammonium uptake carrier of Corynebacterium glutamicum," *J. Biol. Chem.,* 271(10):5398-5403 (1996)
X93514	betP	Glycine betaine transport system	Peter, H. et al. "Isolation, characterization, and expression of the Corynebacterium glutamicum betP gene, encoding the transport system for the compatible solute glycine betaine," *J. Bacteriol.,* 178(17):5229-5234 (1996)
X95649	orf4		Patek, M. et al. "Identification and transcriptional analysis of the dapB-ORF2-dapA-ORF4 operon of Corynebacterium glutamicum, encoding two enzymes involved in L-lysine synthesis," *Biotechnol. Lett.,* 19:1113-1117 (1997)
X96471	lysE; lysG	Lysine exporter protein; Lysine export regulator protein	Vrljic, M. et al. "A new type of transporter with a new type of cellular function: L-lysine export from Corynebacterium glutamicum," *Mol. Microbiol.,* 22(5):815-826 (1996)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
X96580	panB; panC; xylB	3-methyl-2-oxobutanoate hydroxymethyltransferase; pantoate-beta-alanine ligase; xylulokinase	Sahm, H. et al. "D-pantothenate synthesis in Corynebacterium glutamicum and use of panBC and genes encoding L-valine synthesis for D-pantothenate overproduction," *Appl. Environ. Microbiol.*, 65(5):1973-1979 (1999)
X96962		Insertion sequence IS1207 and transposase	
X99289		Elongation factor P	Ramos, A. et al. "Cloning, sequencing and expression of the gene encoding elongation factor P in the amino-acid producer Brevibacterium lactofermentum (Corynebacterium glutamicum ATCC 13869)," *Gene*, 198:217-222 (1997)
Y00140	thrB	Homoserine kinase	Mateos, L.M. et al. "Nucleotide sequence of the homoserine kinase (thrB) gene of the Brevibacterium lactofermentum," *Nucleic Acids Res.*, 15(9):3922 (1987)
Y00151	ddh	Meso-diaminopimelate D-dehydrogenase (EC 1.4.1.16)	Ishino, S. et al. "Nucleotide sequence of the meso-diaminopimelate D-dehydrogenase gene from Corynebacterium glutamicum," *Nucleic Acids Res.*, 15(9):3917 (1987)
Y00476	thrA	Homoserine dehydrogenase	Mateos, L.M. et al. "Nucleotide sequence of the homoserine dehydrogenase (thrA) gene of the Brevibacterium lactofermentum," *Nucleic Acids Res.*, 15(24):10598 (1987)
Y00546	hom; thrB	Homoserine dehydrogenase; homoserine kinase	Peoples, O.P. et al. "Nucleotide sequence and fine structural analysis of the Corynebacterium glutamicum hom-thrB operon," *Mol. Microbiol.*, 2(1):63-72 (1988)
Y08964	murC; ftsQ/divD; ftsZ	UPD-N-acetylmuramate-alanine ligase; division initiation protein or cell division protein; cell division protein	Honrubia, M.P. et al. "Identification, characterization, and chromosomal organization of the ftsZ gene from Brevibacterium lactofermentum," *Mol. Gen. Genet.*, 259(1):97-104 (1998)
Y09163	putP	High affinity proline transport system	Peter, H. et al. "Isolation of the putP gene of Corynebacterium glutamicumproline and characterization of a low-affinity uptake system for compatible solutes," *Arch. Microbiol.*, 168(2):143-151 (1997)
Y09548	pyc	Pyruvate carboxylase	Peters-Wendisch, P.G. et al. "Pyruvate carboxylase from Corynebacterium glutamicum: characterization, expression and inactivation of the pyc gene," *Microbiology*, 144:915-927 (1998)
Y09578	leuB	3-isopropylmalate dehydrogenase	Patek, M. et al. "Analysis of the leuB gene from Corynebacterium glutamicum," *Appl. Microbiol. Biotechnol.*, 50(1):42-47 (1998)
Y12472		Attachment site bacteriophage Phi-16	Moreau, S. et al. "Site-specific integration of corynephage Phi-16: The construction of an integration vector," *Microbiol.*, 145:539-548 (1999)

GenBank™ Accession No.	Gene Name	Gene Function	Reference
Y12537	proP	Proline/ectoine uptake system protein	Peter, H. et al. "Corynebacterium glutamicum is equipped with four secondary carriers for compatible solutes: Identification, sequencing, and characterization of the proline/ectoine uptake system, ProP, and the ectoine/proline/glycine betaine carrier, EctP," *J. Bacteriol.*, 180(22):6005-6012 (1998)
Y13221	glnA	Glutamine synthetase I	Jakoby, M. et al. "Isolation of Corynebacterium glutamicum glnA gene encoding glutamine synthetase I," *FEMS Microbiol. Lett.*, 154(1):81-88 (1997)
Y16642	lpd	Dihydrolipoamide dehydrogenase	
Y18059		Attachment site Corynephage 304L	Moreau, S. et al. "Analysis of the integration functions of φ304L: An integrase module among corynephages," *Virology*, 255(1):150-159 (1999)
Z21501	argS; lysA	Arginyl-tRNA synthetase; diaminopimelate decarboxylase (partial)	Oguiza, J.A. et al. "A gene encoding arginyl-tRNA synthetase is located in the upstream region of the lysA gene in Brevibacterium lactofermentum: Regulation of argS-lysA cluster expression by arginine," *J. Bacteriol.*,175(22):7356-7362 (1993)
Z21502	dapA; dapB	Dihydrodipicolinate synthase; dihydrodipicolinate reductase	Pisabarro, A. et al. "A cluster of three genes (dapA, orf2, and dapB) of Brevibacterium lactofermentum encodes dihydrodipicolinate reductase, and a third polypeptide of unknown function," *J. Bacteriol.*, 175(9):2743-2749 (1993)
Z29563	thrC	Threonine synthase	Malumbres, M. et al. "Analysis and expression of the thrC gene of the encoded threonine synthase," *Appl. Environ. Microbiol.*, 60(7)2209-2219 (1994)
Z46753	16S rDNA	Gene for 16S ribosomal RNA	
Z49822	sigA	SigA sigma factor	Oguiza, J.A. et al "Multiple sigma factor genes in Brevibacterium lactofermentum: Characterization of sigA and sigB," *J. Bacteriol.*, 178(2):550-553 (1996)
Z49823	galE; dtxR	Catalytic activity UDP-galactose 4-epimerase; diphtheria toxin regulatory protein	Oguiza, J.A. et al "The galE gene encoding the UDP-galactose 4-epimerase of Brevibacterium lactofermentum is coupled transcriptionally to the dmdR gene," *Gene*, 177:103-107 (1996)
Z49824	orf1; sigB	?; SigB sigma factor	Oguiza, J.A. et al "Multiple sigma factor genes in Brevibacterium lactofermentum: Characterization of sigA and sigB," *J. Bacteriol.*, 178(2):550-553 (1996)
Z66534		Transposase	Correia, A. et al. "Cloning and characterization of an IS-like element present in the genome of Brevibacterium lactofermentum ATCC 13869," *Gene*, 170(1):91-94 (1996)

[1] A sequence for this gene was published in the indicated reference. However, the sequence obtained by the inventors of the present application is significantly longer than the published version. It is believed that the published version relied on an incorrect start codon, and thus represents only a fragment of the actual coding region.

TABLE 3: Corynebacterium and Brevibacterium Strains Which May be Used in the Practice of the Invention

Genus	species	ATCC	FERM	NRRL	CECT	NCIMB	CBS	NCTC	DSMZ
Brevibacterium	ammoniagenes	21054							
Brevibacterium	ammoniagenes	19350							
Brevibacterium	ammoniagenes	19351							
Brevibacterium	ammoniagenes	19352							
Brevibacterium	ammoniagenes	19353							
Brevibacterium	ammoniagenes	19354							
Brevibacterium	ammoniagenes	19355							
Brevibacterium	ammoniagenes	19356							
Brevibacterium	ammoniagenes	21055							
Brevibacterium	ammoniagenes	21077							
Brevibacterium	ammoniagenes	21553							
Brevibacterium	ammoniagenes	21580							
Brevibacterium	ammoniagenes	39101							
Brevibacterium	butanicum	21196							
Brevibacterium	divaricatum	21792	P928						
Brevibacterium	flavum	21474							
Brevibacterium	flavum	21129							
Brevibacterium	flavum	21518							
Brevibacterium	flavum			B11474					
Brevibacterium	flavum			B11472					
Brevibacterium	flavum	21127							
Brevibacterium	flavum	21128							
Brevibacterium	flavum	21427							
Brevibacterium	flavum	21475							
Brevibacterium	flavum	21517							
Brevibacterium	flavum	21528							
Brevibacterium	flavum	21529							

Brevibacterium	flavum			B11477					
Brevibacterium	flavum			B11478					
Brevibacterium	flavum	21127							
Brevibacterium	flavum			B11474					
Brevibacterium	healii	15527							
Brevibacterium	ketoglutamicum	21004							
Brevibacterium	ketoglutamicum	21089							
Brevibacterium	ketosoreductum	21914							
Brevibacterium	lactofermentum				70				
Brevibacterium	lactofermentum				74				
Brevibacterium	lactofermentum				77				
Brevibacterium	lactofermentum	21798							
Brevibacterium	lactofermentum	21799							
Brevibacterium	lactofermentum	21800							
Brevibacterium	lactofermentum	21801							
Brevibacterium	lactofermentum			B11470					
Brevibacterium	lactofermentum			B11471					
Brevibacterium	lactofermentum	21086							
Brevibacterium	lactofermentum	21420							
Brevibacterium	lactofermentum	21086							
Brevibacterium	lactofermentum	31269							
Brevibacterium	linens	9174							
Brevibacterium	linens	19391							
Brevibacterium	linens	8377							
Brevibacterium	paraffinolyticum					11160			
Brevibacterium	spec.						717.73		
Brevibacterium	spec.						717.73		
Brevibacterium	spec.	14604							
Brevibacterium	spec.	21860							
Brevibacterium	spec.	21864							
Brevibacterium	spec.	21865							

Brevibacterium	spec.	21866							
Brevibacterium	spec.	19240							
Corynebacterium	acetoacidophilum	21476							
Corynebacterium	acetoacidophilum	13870							
Corynebacterium	acetoglutamicum			B11473					
Corynebacterium	acetoglutamicum			B11475					
Corynebacterium	acetoglutamicum	15806							
Corynebacterium	acetoglutamicum	21491							
Corynebacterium	acetoglutamicum	31270							
Corynebacterium	acetophilum			B3671					
Corynebacterium	ammoniagenes	6872						2399	
Corynebacterium	ammoniagenes	15511							
Corynebacterium	fujiokense	21496							
Corynebacterium	glutamicum	14067							
Corynebacterium	glutamicum	39137							
Corynebacterium	glutamicum	21254							
Corynebacterium	glutamicum	21255							
Corynebacterium	glutamicum	31830							
Corynebacterium	glutamicum	13032							
Corynebacterium	glutamicum	14305							
Corynebacterium	glutamicum	15455							
Corynebacterium	glutamicum	13058							
Corynebacterium	glutamicum	13059							
Corynebacterium	glutamicum	13060							
Corynebacterium	glutamicum	21492							
Corynebacterium	glutamicum	21513							
Corynebacterium	glutamicum	21526							
Corynebacterium	glutamicum	21543							
Corynebacterium	glutamicum	13287							
Corynebacterium	glutamicum	21851							
Corynebacterium	glutamicum	21253							

Corynebacterium	glutamicum	21514							
Corynebacterium	glutamicum	21516							
Corynebacterium	glutamicum	21299							
Corynebacterium	glutamicum	21300							
Corynebacterium	glutamicum	39684							
Corynebacterium	glutamicum	21488							
Corynebacterium	glutamicum	21649							
Corynebacterium	glutamicum	21650							
Corynebacterium	glutamicum	19223							
Corynebacterium	glutamicum	13869							
Corynebacterium	glutamicum	21157							
Corynebacterium	glutamicum	21158							
Corynebacterium	glutamicum	21159							
Corynebacterium	glutamicum	21355							
Corynebacterium	glutamicum	31808							
Corynebacterium	glutamicum	21674							
Corynebacterium	glutamicum	21562							
Corynebacterium	glutamicum	21563							
Corynebacterium	glutamicum	21564							
Corynebacterium	glutamicum	21565							
Corynebacterium	glutamicum	21566							
Corynebacterium	glutamicum	21567							
Corynebacterium	glutamicum	21568							
Corynebacterium	glutamicum	21569							
Corynebacterium	glutamicum	21570							
Corynebacterium	glutamicum	21571							
Corynebacterium	glutamicum	21572							
Corynebacterium	glutamicum	21573							
Corynebacterium	glutamicum	21579							
Corynebacterium	glutamicum	19049							
Corynebacterium	glutamicum	19050							

Corynebacterium	glutamicum	19051							
Corynebacterium	glutamicum	19052							
Corynebacterium	glutamicum	19053							
Corynebacterium	glutamicum	19054							
Corynebacterium	glutamicum	19055							
Corynebacterium	glutamicum	19056							
Corynebacterium	glutamicum	19057							
Corynebacterium	glutamicum	19058							
Corynebacterium	glutamicum	19059							
Corynebacterium	glutamicum	19060							
Corynebacterium	glutamicum	19185							
Corynebacterium	glutamicum	13286							
Corynebacterium	glutamicum	21515							
Corynebacterium	glutamicum	21527							
Corynebacterium	glutamicum	21544							
Corynebacterium	glutamicum	21492							
Corynebacterium	glutamicum			B8183					
Corynebacterium	glutamicum			B8182					
Corynebacterium	glutamicum			B12416					
Corynebacterium	glutamicum			B12417					
Corynebacterium	glutamicum			B12418					
Corynebacterium	glutamicum			B11476					
Corynebacterium	glutamicum	21608							
Corynebacterium	lilium		P973						
Corynebacterium	nitrilophilus	21419				11594			
Corynebacterium	spec.		P4445						
Corynebacterium	spec.		P4446						
Corynebacterium	spec.	31088							
Corynebacterium	spec.	31089							
Corynebacterium	spec.	31090							
Corynebacterium	spec.	31090							

Corynebacterium	spec.	31090							
Corynebacterium	spec.	15954							20145
Corynebacterium	spec.	21857							
Corynebacterium	spec.	21862							
Corynebacterium	spec.	21863							

ATCC: American Type Culture Collection, Rockville, MD, USA

FERM: Fermentation Research Institute, Chiba, Japan

NRRL: ARS Culture Collection, Northern Regional Research Laboratory, Peoria, IL, USA

CECT: Coleccion Espanola de Cultivos Tipo, Valencia, Spain

NCIMB: National Collection of Industrial and Marine Bacteria Ltd., Aberdeen, UK

CBS: Centraalbureau voor Schimmelcultures, Baarn, NL

NCTC: National Collection of Type Cultures, London, UK

DSMZ: Deutsche Sammlung von Mikroorganismen und Zellkulturen, Braunschweig, Germany

For reference see Sugawara, H. et al. (1993) World directory of collections of cultures of microorganisms: Bacteria, fungi and yeasts (4th edn), World federation for culture collections world data center on microorganisms, Saimata, Japen.

TABLE 4: ALIGNMENT RESULTS

ID #	length (NT)	Genbank Hit	Length	Accession	Name of Genbank Hit	Source of Genbank Hit	% homology (GAP)	Date of Deposit
rxa00013	996	GB_GSS4:AQ713475	581	AQ713475	HS_5402_B2_A12_T7A RPCI-11 Human Male BAC Library Homo sapiens genomic clone Plate=978 Col=24 Row=B, genomic survey sequence.	Homo sapiens	37,148	13-Jul-99
		GB_HTG3:AC007420	130583	AC007420	Drosophila melanogaster chromosome 2 clone BACR07M10 (D630) RPCI-98 07.M.10 map 24A-24D strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 83 unordered pieces.	Drosophila melanogaster	34,568	20-Sep-99
		GB_HTG3:AC007420	130583	AC007420	Drosophila melanogaster chromosome 2 clone BACR07M10 (D630) RPCI-98 07.M.10 map 24A-24D strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 83 unordered pieces.	Drosophila melanogaster	34,568	20-Sep-99
rxa00014	903	GB_BA1:MTCY3A2	25830	Z83867	Mycobacterium tuberculosis H37Rv complete genome; segment 136/162.	Mycobacterium tuberculosis	58,140	17-Jun-98
		GB_BA1:MLCB1779	43254	Z98271	Mycobacterium leprae cosmid B1779.	Mycobacterium leprae	57,589	8-Aug-97
		GB_BA1:SAPURCLUS	9120	X92429	S.alboniger napH, pur7, pur10, pur6, pur4, pur5 and pur3 genes.	Streptomyces anulatus	55,667	28-Feb-96
rxa00030	513	GB_EST21:C89713	767	C89713	C89713 Dictyostelium discoideum SS (H.Urushihara) Dictyostelium discoideum cDNA clone SSG229, mRNA sequence.	Dictyostelium discoideum	45,283	20-Apr-98
		GB_EST28:AI497294	484	AI497294	fb63g03.y1 Zebrafish WashU MPIMG EST Danio rerio cDNA 5' similar to SW:AFP4_MYOOC P80961 ANTIFREEZE PROTEIN LS-12. ;, mRNA sequence.	Danio rerio	42,991	11-MAR-1999
		GB_EST21:C92167	637	C92167	C92167 Dictyostelium discoideum SS (H.Urushihara) Dictyostelium discoideum cDNA clone SSD179, mRNA sequence.	Dictyostelium discoideum	44,444	12-Jul-99
rxa00032	1632	GB_BA2:AF010496	189370	AF010496	Rhodobacter capsulatus strain SB1003, partial genome.	Rhodobacter capsulatus	39,689	12-MAY-1998
		GB_BA2:AF018073	9810	AF018073	Rhodobacter sphaeroides operon regulator (smoC), periplasmic sorbitol-binding protein (smoE), sorbitol/mannitol transport inner membrane protein (smoF), sorbitol/mannitol transport inner membrane protein (smoG), sorbitol/mannitol transport ATP-binding transport protein (smoK), sorbitol dehydrogenase (smoS), mannitol dehydrogenase (mtlK), and periplasmic mannitol-binding protein (smoM) genes, complete cds.	Rhodobacter sphaeroides	48,045	22-OCT-1997
		GB_BA2:AF045245	5930	AF045245	Klebsiella pneumoniae D-arabinitol transporter (dalT), D-arabinitol kinase (dalK), D-arabinitol dehydrogenase (dalD), and repressor (dalR) genes, complete cds.	Klebsiella pneumoniae	38,514	16-Jul-98
rxa00041	1342	EM_PAT:E11760	6911	E11760	Base sequence of sucrase gene.	Corynebacterium glutamicum	99,031	08-OCT-1997 (Rel. 52, Created)
		GB_PAT:I26124	6911	I26124	Sequence 4 from patent US 5556776.	Unknown.	99,031	07-OCT-1996
		GB_IN1:LMFL5883	31934	AL117384	Leishmania major Friedlin chromosome 23 cosmid L5883, complete sequence.	Leishmania major	43,663	21-OCT-1999
rxa00042	882	EM_PAT:E11760	6911	E11760	Base sequence of sucrase gene.	Corynebacterium glutamicum	94,767	08-OCT-1997 (Rel. 52, Created)
		GB_PAT:I26124	6911	I26124	Sequence 4 from patent US 5556776.	Unknown.	94,767	07-OCT-1996
		GB_IN1:CEU33051	4899	U33051	Caenorhabditis elegans sur-2 mRNA, complete cds.	Caenorhabditis elegans	40,276	23-Jan-96
rxa00043	1287	GB_PAT:I26124	6911	I26124	Sequence 4 from patent US 5556776.	Unknown.	97,591	07-OCT-1996
		EM_PAT:E11760	6911	E11760	Base sequence of sucrase gene.	Corynebacterium glutamicum	97,591	08-OCT-1997 (Rel. 52, Created)
		GB_PR3:AC005174	39769	AC005174	Homo sapiens clone UWGC:g1564a012 from 7p14-15, complete sequence.	Homo sapiens	35,879	24-Jun-98

TABLE 4: ALIGNMENT RESULTS

rxa00098	1743	GB_BA1:MSU88433	1928	U88433	Mycobacterium smegmatis phosphoglucose isomerase gene, complete cds.	Mycobacterium smegmatis	62,658	19-Apr-97
		GB_BA1:SC5A7	40337	AL031107	Streptomyces coelicolor cosmid 5A7.	Streptomyces coelicolor	37,638	27-Jul-98
		GB_BA1:MTCY10D7	39800	Z79700	Mycobacterium tuberculosis H37Rv complete genome; segment 44/162.	Mycobacterium tuberculosis	36,784	17-Jun-98
rxa00148	2334	GB_BA1:MTCY277	38300	Z79701	Mycobacterium tuberculosis H37Rv complete genome; segment 65/162.	Mycobacterium tuberculosis	67,457	17-Jun-98
		GB_BA1:MSGY456	37316	AD000001	Mycobacterium tuberculosis sequence from clone y456.	Mycobacterium tuberculosis	40,883	03-DEC-1996
		GB_BA1:MSGY175	18106	AD000015	Mycobacterium tuberculosis sequence from clone y175.	Mycobacterium tuberculosis	67,457	10-DEC-1996
rxa00149	1971	GB_BA1:MSGY456	37316	AD000001	Mycobacterium tuberculosis sequence from clone y456.	Mycobacterium tuberculosis	35,883	03-DEC-1996
		GB_BA1:MSGY175	18106	AD000015	Mycobacterium tuberculosis sequence from clone y175.	Mycobacterium tuberculosis	51,001	10-DEC-1996
		GB_BA1:MTCY277	38300	Z79701	Mycobacterium tuberculosis H37Rv complete genome; segment 65/162.	Mycobacterium tuberculosis	51,001	17-Jun-98
rxa00195	684	GB_BA1:MTCY274	39991	Z74024	Mycobacterium tuberculosis H37Rv complete genome; segment 126/162.	Mycobacterium tuberculosis	35,735	19-Jun-98
		GB_BA1:MSGB1529CS	36985	L78824	Mycobacterium leprae cosmid B1529 DNA sequence.	Mycobacterium leprae	57,014	15-Jun-96
		GB_BA1:MTCY274	39991	Z74024	Mycobacterium tuberculosis H37Rv complete genome; segment 126/162.	Mycobacterium tuberculosis	41,892	19-Jun-98
rxa00196	738	GB_BA1:MTCY274	39991	Z74024	Mycobacterium tuberculosis H37Rv complete genome; segment 126/162.	Mycobacterium tuberculosis	41,841	19-Jun-98
		GB_BA1:MTCY274	39991	Z74024	Mycobacterium tuberculosis H37Rv complete genome; segment 126/162.	Mycobacterium tuberculosis	36,599	19-Jun-98
		GB_RO:RATCBRQ	10752	M55532	Rat carbohydrate binding receptor gene, complete cds.	Rattus norvegicus	36,212	27-Apr-93
rxa00202	1065	GB_EST11:AA253618	313	AA253618	mw95c10.r1 Soares mouse NML Mus musculus cDNA clone IMAGE:678450 5', mRNA sequence.	Mus musculus	38,816	13-MAR-1997
		GB_EST26:AI390284	490	AI390284	mw96a03.y1 Soares mouse NML Mus musculus cDNA clone IMAGE:678508 5' similar to TR:O09171 O09171 BETAINE-HOMOCYSTEINE METHYLTRANSFERASE;, mRNA sequence.	Mus musculus	42,239	2-Feb-99
		GB_EST26:AI390280	467	AI390280	mw95c10.y1 Soares mouse NML Mus musculus cDNA clone IMAGE:678450 5', mRNA sequence.	Mus musculus	37,307	2-Feb-99
rxa00206	1161	GB_BA1:MLCB637	44882	Z99263	Mycobacterium leprae cosmid B637.	Mycobacterium leprae	58,312	17-Sep-97
		GB_BA1:MTV012	70287	AL021287	Mycobacterium tuberculosis H37Rv complete genome; segment 132/162.	Mycobacterium tuberculosis	36,632	23-Jun-99
		GB_BA1:SC6E10	23990	AL109661	Streptomyces coelicolor cosmid 6E10.	Streptomyces coelicolor A3(2)	38,616	5-Aug-99
rxa00224	1074	GB_BA1:BJU32230	1769	U32230	Bradyrhizobium japonicum electron transfer flavoprotein small subunit (etfS) nd large subunit (etfL) genes, complete cds.	Bradyrhizobium japonicum	48,038	25-MAY-1996
		GB_BA1:PDEETFAB	2440	L14864	Paracoccus denitrificans electron transfer flavoprotein alpha and beta subunit genes, complete cds's.	Paracoccus denitrificans	48,351	27-OCT-1993
		GB_HTG3:AC009689	177954	AC009689	Homo sapiens chromosome 4 clone 104_F_7 map 4, LOW-PASS SEQUENCE SAMPLING.	Homo sapiens	38,756	28-Aug-99
rxa00225	909	GB_RO:AF060178	2057	AF060178	Mus musculus heparan sulfate 2-sulfotransferase (Hs2st) mRNA, complete cds.	Mus musculus	39,506	18-Jun-98
		GB_GSS11:AQ325043	734	AQ325043	mgxb0020J01r CUGI Rice Blast BAC Library Magnaporthe grisea genomic clone mgxb0020J01r, genomic survey sequence.	Magnaporthe grisea	38,333	8-Jan-99
		GB_EST31:AI676413	551	AI676413	etmEST0167 EtH1 Eimeria tenella cDNA clone etmc074 5', mRNA sequence.	Eimeria tenella	35,542	19-MAY-1999
rxa00235	1398	GB_BA1:MTCY10G2	38970	Z92539	Mycobacterium tuberculosis H37Rv complete genome; segment 47/162.	Mycobacterium tuberculosis	65,759	17-Jun-98
		GB_BA2:AF061753	3721	AF061753	Nitrosomonas europaea CTP synthase (pyrG) gene, partial cds; and enolase (eno) gene, complete cds.	Nitrosomonas europaea	58,941	31-Aug-98
		GB_BA2:AF086791	37867	AF086791	Zymomonas mobilis strain ZM4 clone 67E10 carbamoylphosphate synthetase small subunit (carA), carbamoylphosphate synthetase large subunit (carB), transcription elongation factor (greA), enolase (eno), pyruvate dehydrogenase alpha subunit (pdhA), pyruvate dehydrogenase beta subunit (pdhB), ribonuclease H (rnh), homoserine kinase homolog, alcohol dehydrogenase II (adhB), and excinuclease ABC subunit A (uvrA) genes, complete cds; and unknown genes.	Zymomonas mobilis	61,239	4-Nov-98
rxa00246	1158	GB_BA2:AF012550	2690	AF012550	Acinetobacter sp. BD413 ComP (comP) gene, complete cds.	Acinetobacter sp. BD413	53,726	27-Sep-99

TABLE 4: ALIGNMENT RESULTS

		GB_PAT:E03856	1506	E03856	gDNA encoding alcohol dehydrogenase.	Bacillus stearothermophilus	51,688	29-Sep-97
		GB_BA1:BACADHT	1688	D90421	B.stearothermophilus adhT gene for alcohol dehydrogenase.	Bacillus stearothermophilus	51,602	7-Feb-99
rxa00251	831	GB_BA1:MTCY20G9	37218	Z77162	Mycobacterium tuberculosis H37Rv complete genome; segment 25/162.	Mycobacterium tuberculosis	42,875	17-Jun-98
		GB_BA1:MTV004	69350	AL009198	Mycobacterium tuberculosis H37Rv complete genome; segment 144/162.	Mycobacterium tuberculosis	40,380	18-Jun-98
		GB_BA1:MTV004	69350	AL009198	Mycobacterium tuberculosis H37Rv complete genome; segment 144/162.	Mycobacterium tuberculosis	41,789	18-Jun-98
rxa00288	1134	GB_BA2:AF050114	1038	AF050114	Pseudomonas sp. W7 alginate lyase gene, complete cds.	Pseudomonas sp. W7	49,898	03-MAR-1999
		GB_GSS3:B16984	469	B16984	344A14.TVC CIT978SKA1 Homo sapiens genomic clone A-344A14, genomic survey sequence.	Homo sapiens	39,355	4-Jun-98
		GB_IN2:AF144549	7887	AF144549	Aedes albopictus ribosomal protein L34 (rpl34) gene, complete cds.	Aedes albopictus	36,509	3-Jun-99
rxa00293	1035	GB_EST1:T28483	313	T28483	EST46182 Human Kidney Homo sapiens cDNA 3' end similar to flavin-containing monooxygenase 1 (HT:1956), mRNA sequence.	Homo sapiens	42,997	6-Sep-95
		GB_PR1:HUMFMO1	2134	M64082	Human flavin-containing monooxygenase (FMO1) mRNA, complete cds.	Homo sapiens	37,915	8-Nov-94
		GB_EST32:AI734238	512	AI734238	zb73c05.y5 Soares_fetal_lung_NbHL19W Homo sapiens cDNA clone IMAGE:309224 5' similar to gb:M64082 DIMETHYLANILINE MONOOXYGENASE (HUMAN);, mRNA sequence.	Homo sapiens	41,502	14-Jun-99
rxa00296	2967	GB_HTG6:AC011069	168266	AC011069	Drosophila melanogaster chromosome X clone BACR11H20 (D881) RPCI-98 11.H.20 map 12B-12C strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 92 unordered pieces.	Drosophila melanogaster	33,890	02-DEC-1999
		GB_EST15:AA531468	414	AA531468	nj63d12.s1 NCI_CGAP_Pr10 Homo sapiens cDNA clone IMAGE:997175, mRNA sequence.	Homo sapiens	40,821	20-Aug-97
		GB_HTG6:AC011069	168266	AC011069	Drosophila melanogaster chromosome X clone BACR11H20 (D881) RPCI-98 11.H.20 map 12B-12C strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 92 unordered pieces.	Drosophila melanogaster	30,963	02-DEC-1999
rxa00310	558	GB_VI:VMVY16780	186986	Y16780	variola minor virus complete genome.	variola minor virus	35,883	2-Sep-99
		GB_VI:VARCG	186103	L22579	Variola major virus (strain Bangladesh-1975) complete genome.	Variola major virus	34,664	12-Jan-95
		GB_VI:VVCGAA	185578	X69198	Variola virus DNA complete genome.	Variola virus	36,000	13-DEC-1996
rxa00317	777	GB_HTG3:AC009571	159648	AC009571	Homo sapiens chromosome 4 clone 57_A_22 map 4, *** SEQUENCING IN PROGRESS ***, 8 unordered pieces.	Homo sapiens	36,988	29-Sep-99
		GB_HTG3:AC009571	159648	AC009571	Homo sapiens chromosome 4 clone 57_A_22 map 4, *** SEQUENCING IN PROGRESS ***, 8 unordered pieces.	Homo sapiens	36,988	29-Sep-99
		GB_PR3:AC005697	174503	AC005697	Homo sapiens chromosome 17, clone hRPK.138_P_22, complete sequence.	Homo sapiens	36,340	09-OCT-1998
rxa00327	507	GB_BA1:LCATPASEB	1514	X64542	L.casei gene for ATPase beta-subunit.	Lactobacillus casei	34,664	11-DEC-1992
		GB_BA1:LCATPASEB	1514	X64542	L.casei gene for ATPase beta-subunit.	Lactobacillus casei	39,308	11-DEC-1992
rxa00328	615	GB_BA1:STYPUTPE	1887	L01138	Salmonella (S2980) proline permease (putP) gene, 5' end.	Salmonella sp.	39,623	09-MAY-1996
		GB_BA1:STYPUTPF	1887	L01139	Salmonella (S2983) proline permease (putP) gene, 5' end.	Salmonella sp.	39,623	09-MAY-1996
		GB_BA1:STYPUTPI	1889	L01142	Salmonella (S3015) proline permease (putP) gene, 5' end.	Salmonella sp.	42,906	09-MAY-1996
rxa00329	1347	GB_PR3:AC004691	141990	AC004691	Homo sapiens PAC clone DJ0740D02 from 7p14-p15, complete sequence.	Homo sapiens	38,142	16-MAY-1998
		GB_PR4:AC004916	129014	AC004916	Homo sapiens clone DJ0891L14, complete sequence.	Homo sapiens	38,549	17-Jul-99
		GB_PR3:AC004691	141990	AC004691	Homo sapiens PAC clone DJ0740D02 from 7p14-p15, complete sequence.	Homo sapiens	35,865	16-MAY-1998
rxa00340	1269	GB_BA1:MTCY427	38110	Z70692	Mycobacterium tuberculosis H37Rv complete genome; segment 99/162.	Mycobacterium tuberculosis	38,940	24-Jun-99
		GB_GSS12:AQ412290	238	AQ412290	RPCI-11-195H2.TV RPCI-11 Homo sapiens genomic clone RPCI-11-195H2, genomic survey sequence.	Homo sapiens	36,555	23-MAR-1999
		GB_PL2:AF112871	2394	AF112871	Astasia longa small subunit ribosomal RNA gene, complete sequence.	Astasia longa	36,465	28-Jun-99

TABLE 4: ALIGNMENT RESULTS

rxa00379	307	GB_HTG1:CEY56A3	224746	AL022280	Caenorhabditis elegans chromosome III clone Y56A3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Caenorhabditis elegans	35,179	6-Sep-99
		GB_HTG1:CEY56A3	224746	AL022280	Caenorhabditis elegans chromosome III clone Y56A3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Caenorhabditis elegans	35,179	6-Sep-99
		GB_PR2:HS134O19	86897	AL034555	Human DNA sequence from clone 134O19 on chromosome 1p36.11-36.33, complete sequence.	Homo sapiens	40,604	23-Nov-99
rxa00381	729	GB_GSS4:AQ730532	416	AQ730532	HS_2149_A1_C06_T7C CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=2149 Col=11 Row=E, genomic survey sequence.	Homo sapiens	35,766	15-Jul-99
		GB_EST23:AI120939	561	AI120939	ub74f05.r1 Soares mouse mammary gland NMLMG Mus musculus cDNA clone IMAGE:1383489 5' similar to gb:J04046 CALMODULIN (HUMAN); gb:M19381 Mouse calmodulin (MOUSE);, mRNA sequence.	Mus musculus	41,113	2-Sep-98
		GB_EST23:AI120939	561	AI120939	ub74f05.r1 Soares mouse mammary gland NMLMG Mus musculus cDNA clone IMAGE:1383489 5' similar to gb:J04046 CALMODULIN (HUMAN); gb:M19381 Mouse calmodulin (MOUSE);, mRNA sequence.	Mus musculus	41,113	2-Sep-98
rxa00385	362	GB_EST32:AI726450	565	AI726450	BNLGHi5857 Six-day Cotton fiber Gossypium hirsutum cDNA 5' similar to (AF015913) Skb1Hs [Homo sapiens], mRNA sequence.	Gossypium hirsutum	41,152	11-Jun-99
		GB_GSS4:AQ740856	768	AQ740856	HS_2274_A2_A07_T7C CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=2274 Col=14 Row=A, genomic survey sequence.	Homo sapiens	41,360	16-Jul-99
		GB_PR1:HSPAIP	1587	X91809	H.sapiens mRNA for GAIP protein.	Homo sapiens	36,792	29-MAR-1996
rxa00388	1134	GB_BA1:MTY25D10	40838	Z95558	Mycobacterium tuberculosis H37Rv complete genome; segment 28/162.	Mycobacterium tuberculosis	51,852	17-Jun-98
		GB_BA1:MSGY224	40051	AD000004	Mycobacterium tuberculosis sequence from clone y224.	Mycobacterium tuberculosis	51,852	03-DEC-1996
		GB_HTG1:AP000471	72466	AP000471	Homo sapiens chromosome 21 clone B2308H15 map 21q22.3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	36,875	13-Sep-99
rxa00427	909	GB_BA1:MSGY126	37164	AD000012	Mycobacterium tuberculosis sequence from clone y126.	Mycobacterium tuberculosis	60,022	10-DEC-1996
		GB_BA1:MTY13D12	37085	Z80343	Mycobacterium tuberculosis H37Rv complete genome; segment 156/162.	Mycobacterium tuberculosis	60,022	17-Jun-98
		GB_HTG1:CEY48C3	270193	Z92855	Caenorhabditis elegans chromosome II clone Y48C3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Caenorhabditis elegans	28,013	29-MAY-1999
rxa00483	1587	GB_PR2:HSAF001550	173882	AF001550	Homo sapiens chromosome 16 BAC clone CIT987SK-334D11 complete sequence.	Homo sapiens	38,226	22-Aug-97
		GB_BA1:LLCPJW565	12828	Y12736	Lactococcus lactis cremoris plasmid pJW565 DNA, abiiM, abiiR genes and orfX.	Lactococcus lactis subsp. cremoris	37,492	01-MAR-1999
		GB_HTG2:AC006754	206217	AC006754	Caenorhabditis elegans clone Y40B10, *** SEQUENCING IN PROGRESS ***, 5 unordered pieces.	Caenorhabditis elegans	36,648	23-Feb-99
rxa00511	615	GB_PR3:HSE127C11	38423	Z74581	Human DNA sequence from cosmid E127C11 on chromosome 22q11.2-qter contains STS.	Homo sapiens	39,831	23-Nov-99
		GB_PR3:HSE127C11	38423	Z74581	Human DNA sequence from cosmid E127C11 on chromosome 22q11.2-qter contains STS.	Homo sapiens	36,409	23-Nov-99
rxa00512	718	GB_BA1:MTCY22G8	22550	Z95585	Mycobacterium tuberculosis H37Rv complete genome; segment 49/162.	Mycobacterium tuberculosis	56,232	17-Jun-98
		GB_BA1:MSGLTA	1776	X60513	M.smegmatis gltA gene for citrate synthase.	Mycobacterium smegmatis	56,143	20-Sep-91
		GB_BA2:ECU73857	128824	U73857	Escherichia coli chromosome minutes 6-8.	Escherichia coli	48,563	14-Jul-99
rxa00517	1164	GB_HTG2:AC006911	298804	AC006911	Caenorhabditis elegans clone Y94H6x, *** SEQUENCING IN PROGRESS ***, 15 unordered pieces.	Caenorhabditis elegans	37,889	24-Feb-99
		GB_HTG2:AC006911	298804	AC006911	Caenorhabditis elegans clone Y94H6x, *** SEQUENCING IN PROGRESS ***, 15 unordered pieces.	Caenorhabditis elegans	37,889	24-Feb-99

TABLE 4: ALIGNMENT RESULTS

		GB_EST29:AI602158	481	AI602158	UI-R-AB0-vy-a-01-0-UI.s2 UI-R-AB0 Rattus norvegicus cDNA clone UI-R-AB0-vy-a-01-0-UI 3', mRNA sequence.	Rattus norvegicus	40,833	21-Apr-99
rxa00518	320	GB_BA2:ECU73857	128824	U73857	Escherichia coli chromosome minutes 6-8.	Escherichia coli	49,688	14-Jul-99
		GB_BA2:STU51879	8371	U51879	Salmonella typhimurium propionate catabolism operon: RpoN activator protein homolog (prpR), carboxyphosphonoenolpyruvate phosphonomutase homolog (prpB), citrate synthase homolog (prpC), prpD and prpE genes, complete cds.	Salmonella typhimurium	50,313	5-Aug-99
		GB_BA2:AE000140	12498	AE000140	Escherichia coli K-12 MG1655 section 30 of 400 of the complete genome.	Escherichia coli	49,688	12-Nov-98
rxa00606	2378	GB_EST32:AU068253	376	AU068253	AU068253 Rice callus Oryza sativa cDNA clone C12658_9A, mRNA sequence.	Oryza sativa	41,333	7-Jun-99
		GB_EST13:AA363046	329	AA363046	EST72922 Ovary II Homo sapiens cDNA 5' end, mRNA sequence.	Homo sapiens	34,347	21-Apr-97
		GB_EST32:AU068253	376	AU068253	AU068253 Rice callus Oryza sativa cDNA clone C12658_9A, mRNA sequence.	Oryza sativa	41,899	7-Jun-99
rxa00635	1860	GB_BA1:PAORF1	1440	X13378	Pseudomonas amyloderamosa DNA for ORF 1.	Pseudomonas amyloderamosa	53,912	14-Jul-95
		GB_BA1:PAORF1	1440	X13378	Pseudomonas amyloderamosa DNA for ORF 1.	Pseudomonas amyloderamosa	54,422	14-Jul-95
rxa00679	1389	GB_PL2:AC010871	80381	AC010871	Arabidopsis thaliana chromosome III BAC T16O11 genomic sequence, complete sequence.	Arabidopsis thaliana	38,244	13-Nov-99
		GB_PL1:AT81KBGEN	81493	X98130	A.thaliana 81kb genomic sequence.	Arabidopsis thaliana	36,091	12-MAR-1997
		GB_PL2:AC010871	80381	AC010871	Arabidopsis thaliana chromosome III BAC T16O11 genomic sequence, complete sequence.	Arabidopsis thaliana	37,135	13-Nov-99
rxa00680	441	GB_PR3:AC004058	38400	AC004058	Homo sapiens chromosome 4 clone B241P19 map 4q25, complete sequence.	Homo sapiens	36,165	30-Sep-98
		GB_PL1:AT81KBGEN	81493	X98130	A.thaliana 81kb genomic sequence.	Arabidopsis thaliana	38,732	12-MAR-1997
		GB_PL1:AB026648	43481	AB026648	Arabidopsis thaliana genomic DNA, chromosome 3, P1 clone: MLJ15, complete sequence.	Arabidopsis thaliana	38,732	07-MAY-1999
rxa00682	2022	GB_HTG3:AC010325	197110	AC010325	Homo sapiens chromosome 19 clone CITB-E1_2568A17, *** SEQUENCING IN PROGRESS ***, 40 unordered pieces.	Homo sapiens	37,976	15-Sep-99
		GB_HTG3:AC010325	197110	AC010325	Homo sapiens chromosome 19 clone CITB-E1_2568A17, *** SEQUENCING IN PROGRESS ***, 40 unordered pieces.	Homo sapiens	37,976	15-Sep-99
		GB_PR4:AC008179	181745	AC008179	Homo sapiens clone NH0576F01, complete sequence.	Homo sapiens	37,143	28-Sep-99
rxa00683	1215	GB_BA2:AE000896	10707	AE000896	Methanobacterium thermoautotrophicum from bases 1189349 to 1200055 (section 102 of 148) of the complete genome.	Methanobacterium thermoautotrophicum	38,429	15-Nov-97
		GB_IN1:DMBR7A4	212734	AL109630	Drosophila melanogaster clone BACR7A4.	Drosophila melanogaster	36,454	30-Jul-99
		GB_EST35:AV163010	273	AV163010	AV163010 Mus musculus head C57BL/6J 13-day embryo Mus musculus cDNA clone 3110006J22, mRNA sequence.	Mus musculus	41,758	8-Jul-99
rxa00686	927	GB_HTG2:HSDJ137K2	190223	AL049820	Homo sapiens chromosome 6 clone RP1-137K2 map q25.1-25.3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	38,031	03-DEC-1999
		GB_HTG2:HSDJ137K2	190223	AL049820	Homo sapiens chromosome 6 clone RP1-137K2 map q25.1-25.3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	38,031	03-DEC-1999
		GB_EST12:AA284399	431	AA284399	zs57b04.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:701551 5', mRNA sequence.	Homo sapiens	39,205	14-Aug-97
rxa00700	927	GB_EST34:AI785570	454	AI785570	uj44d03.x1 Sugano mouse liver mlia Mus musculus cDNA clone IMAGE:1922789 3' similar to gb:Z28407 60S RIBOSOMAL PROTEIN L8 (HUMAN);, mRNA sequence.	Mus musculus	41,943	2-Jul-99

TABLE 4: ALIGNMENT RESULTS

		GB_EST25:AI256147	684	AI256147	ui95e12.x1 Sugano mouse liver mlia Mus musculus cDNA clone IMAGE:1890190 3' similar to gb:Z28407 60S RIBOSOMAL PROTEIN L8 (HUMAN);, mRNA sequence.	Mus musculus	40,791	12-Nov-98
		GB_BA1:CARCG12	2079	X14979	C. aurantiacus reaction center genes 1 and 2.	Chloroflexus aurantiacus	37,721	23-Apr-91
rxa00703	2409	GB_BA1:SC7H2	42655	AL109732	Streptomyces coelicolor cosmid 7H2.	Streptomyces coelicolor A3(2)	56,646	2-Aug-99
		GB_BA1:MTCY274	39991	Z74024	Mycobacterium tuberculosis H37Rv complete genome; segment 126/162.	Mycobacterium tuberculosis	37,369	19-Jun-98
		GB_BA2:REU60056	2520	U60056	Ralstonia eutropha formate dehydrogenase-like protein (cbbBc) gene, complete cds.	Ralstonia eutropha	51,087	16-OCT-1996
rxa00705	1038	GB_GSS15:AQ604477	505	AQ604477	HS_2116_B1_G07_MR CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=2116 Col=13 Row=N, genomic survey sequence.	Homo sapiens	39,617	10-Jun-99
		GB_EST11:AA224340	443	AA224340	zr14e07.s1 Stratagene hNT neuron (#937233) Homo sapiens cDNA clone IMAGE:648804 3', mRNA sequence.	Homo sapiens	35,129	11-MAR-1998
		GB_EST5:N30648	291	N30648	yw77b02.s1 Soares_placenta_8to9weeks_2NbHP8to9W Homo sapiens cDNA clone IMAGE:258219 3', mRNA sequence.	Homo sapiens	43,986	5-Jan-96
rxa00782	1005	GB_BA1:MTCY10D7	39800	Z79700	Mycobacterium tuberculosis H37Rv complete genome; segment 44/162.	Mycobacterium tuberculosis	63,327	17-Jun-98
		GB_BA1:MLCL373	37304	AL035500	Mycobacterium leprae cosmid L373.	Mycobacterium leprae	62,300	27-Aug-99
		GB_BA2:AF128399	2842	AF128399	Pseudomonas aeruginosa succinyl-CoA synthetase beta subunit (sucC) and succinyl CoA synthetase alpha subunit (sucD) genes, complete cds.	Pseudomonas aeruginosa	53,698	25-MAR-1999
rxa00783	1395	GB_HTG2:AC008158	118792	AC008158	Homo sapiens chromosome 17 clone hRPK.42_F_20 map 17, *** SEQUENCING IN PROGRESS ***, 14 unordered pieces.	Homo sapiens	35,135	28-Jul-99
		GB_HTG2:AC008158	118792	AC008158	Homo sapiens chromosome 17 clone hRPK.42_F_20 map 17, *** SEQUENCING IN PROGRESS ***, 14 unordered pieces.	Homo sapiens	35,135	28-Jul-99
		GB_PR3:AC005017	137176	AC005017	Homo sapiens BAC clone GS214N13 from 7p14-p15, complete sequence.	Homo sapiens	35,864	8-Aug-98
rxa00794	1128	GB_BA1:MTV017	67200	AL021897	Mycobacterium tuberculosis H37Rv complete genome; segment 48/162.	Mycobacterium tuberculosis	40,331	24-Jun-99
		GB_BA1:MLCB1222	34714	AL049491	Mycobacterium leprae cosmid B1222.	Mycobacterium leprae	61,170	27-Aug-99
		GB_PR2:HS151B14	128942	Z82188	Human DNA sequence from clone 151B14 on chromosome 22 Contains SOMATOSTATIN RECEPTOR TYPE 3 (SS3R) gene,pseudogene similar to ribosomal protein L39,RAC2 (RAS-RELATED C3 BOTULINUM TOXIN SUBSTRATE 2 (P21-RAC2)) gene ESTs, STSs, GSSs and CpG islands, complete sequence.	Homo sapiens	37,455	16-Jun-99
rxa00799	1767	GB_PL2:AF016327	616	AF016327	Hordeum vulgare Barperm1 (perm1) mRNA, partial cds.	Hordeum vulgare	41,311	01-OCT-1997
		GB_HTG2:HSDJ319M7	128208	AL079341	Homo sapiens chromosome 6 clone RP1-319M7 map p21.1-21.3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	36,845	30-Nov-99
		GB_HTG2:HSDJ319M7	128208	AL079341	Homo sapiens chromosome 6 clone RP1-319M7 map p21.1-21.3, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	36,845	30-Nov-99
rxa00800	1227	GB_BA1:MTV022	13025	AL021925	Mycobacterium tuberculosis H37Rv complete genome; segment 100/162.	Mycobacterium tuberculosis	63,101	17-Jun-98
		GB_BA1:AB019513	4417	AB019513	Streptomyces coelicolor genes for alcohol dehydrogenase and ABC transporter, complete cds.	Streptomyces coelicolor	41,312	13-Nov-98
		GB_PL1:SCSFAARP	7008	X68020	S.cerevisiae SFA and ARP genes.	Saccharomyces cerevisiae	36,288	29-Nov-94
rxa00825	1056	GB_BA1:MTY15C10	33050	Z95436	Mycobacterium tuberculosis H37Rv complete genome; segment 154/162.	Mycobacterium tuberculosis	39,980	17-Jun-98
		GB_BA1:MLCB2548	38916	AL023093	Mycobacterium leprae cosmid B2548.	Mycobacterium leprae	39,435	27-Aug-99
		GB_BA2:AF169031	1141	AF169031	Xanthomonas oryzae pv. oryzae putative sugar nucleotide epimerase/dehydratase gene, partial cds.	Xanthomonas oryzae pv. oryzae	46,232	14-Sep-99
rxa00871								

TABLE 4: ALIGNMENT RESULTS

rxa00872	1077	GB_IN1:CEF23H12	35564	Z74472	Caenorhabditis elegans cosmid F23H12, complete sequence.	Caenorhabditis elegans	34,502	08-OCT-1999
		GB_HTG2:AC007263	167390	AC007263	Homo sapiens chromosome 14 clone BAC 79J20 map 14q31, *** SEQUENCING IN PROGRESS ***, 5 ordered pieces.	Homo sapiens	35,714	24-MAY-1999
		GB_HTG2:AC007263	167390	AC007263	Homo sapiens chromosome 14 clone BAC 79J20 map 14q31, *** SEQUENCING IN PROGRESS ***, 5 ordered pieces.	Homo sapiens	35,714	24-MAY-1999
rxa00879	2241	GB_BA1:MTV049	40360	AL022021	Mycobacterium tuberculosis H37Rv complete genome; segment 81/162.	Mycobacterium tuberculosis	36,981	19-Jun-98
		GB_PL2:CDU236897	1827	AJ236897	Candida dubliniensis ACT1 gene, exons 1-2.	Candida dubliniensis	38,716	1-Sep-99
		GB_PL1:CAACT1A	3206	X16377	Candida albicans act1 gene for actin.	Candida albicans	36,610	10-Apr-93
rxa00909	955	GB_BA2:AF010496	189370	AF010496	Rhodobacter capsulatus strain SB1003, partial genome.	Rhodobacter capsulatus	51,586	12-MAY-1998
		GB_BA1:RMPHA	7888	X93358	Rhizobium meliloti pha[A,B,C,D,E,F,G] genes.	Sinorhizobium meliloti	48,367	12-MAR-1999
		GB_EST16:C23528	317	C23528	C23528 Japanese flounder spleen Paralichthys olivaceus cDNA clone HB5(2), mRNA sequence.	Paralichthys olivaceus	41,640	28-Sep-99
rxa00913	2118	GB_HTG2:AC007734	188267	AC007734	Homo sapiens chromosome 18 clone hRPK.44_O_1 map 18, *** SEQUENCING IN PROGRESS ***, 18 unordered pieces.	Homo sapiens	34,457	5-Jun-99
		GB_HTG2:AC007734	188267	AC007734	Homo sapiens chromosome 18 clone hRPK.44_O_1 map 18, *** SEQUENCING IN PROGRESS ***, 18 unordered pieces.	Homo sapiens	34,457	5-Jun-99
		GB_EST18:AA709478	406	AA709478	vv34a05.r1 Stratagene mouse heart (#937316) Mus musculus cDNA clone IMAGE:1224272 5', mRNA sequence.	Mus musculus	42,065	24-DEC-1997
rxa00945	1095	GB_HTG4:AC010351	220710	AC010351	Homo sapiens chromosome 5 clone CITB-H1_2022B6, *** SEQUENCING IN PROGRESS ***, 68 unordered pieces.	Homo sapiens	36,448	31-OCT-1999
		GB_HTG4:AC010351	220710	AC010351	Homo sapiens chromosome 5 clone CITB-H1_2022B6, *** SEQUENCING IN PROGRESS ***, 68 unordered pieces.	Homo sapiens	36,448	31-OCT-1999
		GB_BA1:MTCY05A6	38631	Z96072	Mycobacterium tuberculosis H37Rv complete genome; segment 120/162.	Mycobacterium tuberculosis	36,218	17-Jun-98
rxa00965								
rxa00999	1575	GB_PAT:E13660	1916	E13660	gDNA encoding 6-phosphogluconate dehydrogenase.	Corynebacterium glutamicum	98,349	24-Jun-98
		GB_BA1:MTCY359	36021	Z83859	Mycobacterium tuberculosis H37Rv complete genome; segment 84/162.	Mycobacterium tuberculosis	38,520	17-Jun-98
		GB_BA1:MLCB1788	39228	AL008609	Mycobacterium leprae cosmid B1788.	Mycobacterium leprae	64,355	27-Aug-99
rxa01015	442	GB_BA1:MTV008	63033	AL021246	Mycobacterium tuberculosis H37Rv complete genome; segment 108/162.	Mycobacterium tuberculosis	39,860	17-Jun-98
		GB_BA1:MTV008	63033	AL021246	Mycobacterium tuberculosis H37Rv complete genome; segment 108/162.	Mycobacterium tuberculosis	39,120	17-Jun-98
rxa01025	1119	GB_BA1:SC7A1	32039	AL034447	Streptomyces coelicolor cosmid 7A1.	Streptomyces coelicolor	55,287	15-DEC-1998
		GB_BA1:MSGB1723CS	38477	L78825	Mycobacterium leprae cosmid B1723 DNA sequence.	Mycobacterium leprae	56,847	15-Jun-96
		GB_BA1:MLCB637	44882	Z99263	Mycobacterium leprae cosmid B637.	Mycobacterium leprae	56,676	17-Sep-97
rxa01048	1347	GB_BA2:AF017444	3067	AF017444	Sinorhizobium meliloti NADP-dependent malic enzyme (tme) gene, complete cds.	Sinorhizobium meliloti	53,660	2-Nov-97
		GB_BA1:BSUB0013	218470	Z99116	Bacillus subtilis complete genome (section 13 of 21): from 2395261 to 2613730.	Bacillus subtilis	37,255	26-Nov-97
		GB_VI:HSV2HG52	154746	Z86099	Herpes simplex virus type 2 (strain HG52), complete genome.	human herpesvirus 2	38,081	04-DEC-1998
rxa01049	1605	GB_HTG2:AC002518	131855	AC002518	Homo sapiens chromosome X clone bWXD20, *** SEQUENCING IN PROGRESS ***, 11 unordered pieces.	Homo sapiens	35,647	2-Sep-97
		GB_HTG2:AC002518	131855	AC002518	Homo sapiens chromosome X clone bWXD20, *** SEQUENCING IN PROGRESS ***, 11 unordered pieces.	Homo sapiens	35,647	2-Sep-97

TABLE 4: ALIGNMENT RESULTS

		GB_HTG2:AC002518	131855	AC002518	Homo sapiens chromosome X clone bWXD20, *** SEQUENCING IN PROGRESS ***, 11 unordered pieces.	Homo sapiens	26,180	2-Sep-97
rxa01077	1494	GB_PR3:HSDJ653C5	85237	AL049743	Human DNA sequence from clone 653C5 on chromosome 1p21.3-22.3 Contains CA repeat(D1S435), STSs and GSSs, complete sequence.	Homo sapiens	36,462	23-Nov-99
		GB_BA1:ECU29579	72221	U29579	Escherichia coli K-12 genome; approximately 61 to 62 minutes.	Escherichia coli	41,808	1-Jul-95
		GB_BA1:ECU29579	72221	U29579	Escherichia coli K-12 genome; approximately 61 to 62 minutes.	Escherichia coli	36,130	1-Jul-95
rxa01089	873	GB_GSS8:AQ044021	387	AQ044021	CIT-HSP-2318C18.TR CIT-HSP Homo sapiens genomic clone 2318C18, genomic survey sequence.	Homo sapiens	36,528	14-Jul-98
		GB_GSS8:AQ042907	392	AQ042907	CIT-HSP-2318D17.TR CIT-HSP Homo sapiens genomic clone 2318D17, genomic survey sequence.	Homo sapiens	35,969	14-Jul-98
		GB_GSS8:AQ044021	387	AQ044021	CIT-HSP-2318C18.TR CIT-HSP Homo sapiens genomic clone 2318C18, genomic survey sequence.	Homo sapiens	44,545	14-Jul-98
rxa01093	1554	GB_BA1:CORPYKI	2795	L27126	Corynebacterium pyruvate kinase gene, complete cds.	Corynebacterium glutamicum	100,000	07-DEC-1994
		GB_BA1:MTCY01B2	35938	Z95554	Mycobacterium tuberculosis H37Rv complete genome; segment 72/162.	Mycobacterium tuberculosis	63,771	17-Jun-98
		GB_BA1:MIU65430	1439	U65430	Mycobacterium intracellulare pyruvate kinase (pykF) gene, complete cds.	Mycobacterium intracellulare	67,061	23-DEC-1996
rxa01099	948	GB_BA2:AF045998	780	AF045998	Corynebacterium glutamicum inositol monophosphate phosphatase (impA) gene, complete cds.	Corynebacterium glutamicum	99,615	19-Feb-98
		GB_BA2:AF051846	738	AF051846	Corynebacterium glutamicum phosphoribosylformimino-5-amino-1-phosphoribosyl-4-imidazolecarboxamide isomerase (hisA) gene, complete cds.	Corynebacterium glutamicum	100,000	12-MAR-1998
		GB_GSS1:FR0005503	619	Z89313	F.rubripes GSS sequence, clone 079B16aE8, genomic survey sequence.	Fugu rubripes	37,785	01-MAR-1997
rxa01111	541	GB_PR3:AC004063	177014	AC004063	Homo sapiens chromosome 4 clone B32I8, complete sequence.	Homo sapiens	35,835	10-Jul-98
		GB_PR3:HS1178I21	62268	AL109852	Human DNA sequence from clone RP5-1178I21 on chromosome X, complete sequence.	Homo sapiens	37,873	01-DEC-1999
		GB_HTG3:AC009301	163369	AC009301	Homo sapiens clone NH0062F14, *** SEQUENCING IN PROGRESS ***, 5 unordered pieces.	Homo sapiens	37,240	13-Aug-99
rxa01130	687	GB_HTG3:AC009444	164587	AC009444	Homo sapiens clone 1_O_3, *** SEQUENCING IN PROGRESS ***, 8 unordered pieces.	Homo sapiens	38,416	22-Aug-99
		GB_HTG3:AC009444	164587	AC009444	Homo sapiens clone 1_O_3, *** SEQUENCING IN PROGRESS ***, 8 unordered pieces.	Homo sapiens	38,416	22-Aug-99
		GB_IN1:DMC66A1	34127	AL031227	Drosophila melanogaster cosmid 66A1.	Drosophila melanogaster	38,416	05-OCT-1998
rxa01193	1572	GB_BA1:CGASO19	1452	X76875	C.glutamicum (ASO 19) ATPase beta-subunit gene.	Corynebacterium glutamicum	99,931	27-OCT-1994
		EM_PAT:E09634	1452	E09634	Brevibacterium flavum UncD gene whose gene product is involved in	Corynebacterium glutamicum	99,242	07-OCT-1997 (Rel. 52, Created)
		GB_BA1:MLU15186	36241	U15186	Mycobacterium leprae cosmid L471.	Mycobacterium leprae	39,153	09-MAR-1995
rxa01194	495	EM_PAT:E09634	1452	E09634	Brevibacterium flavum UncD gene whose gene product is involved in	Corynebacterium glutamicum	100,000	07-OCT-1997 (Rel. 52, Created)
		GB_BA1:CGASO19	1452	X76875	C.glutamicum (ASO 19) ATPase beta-subunit gene.	Corynebacterium glutamicum	100,000	27-OCT-1994
rxa01200		GB_VI:HEPCRE4B	414	X60570	Hepatitis C genomic RNA for putative envelope protein (RE4B isolate).	Hepatitis C virus	36,769	5-Apr-92
rxa01201	1764	GB_BA1:SLATPSYNA	8560	Z22606	S.lividans i protein and ATP synthase genes.	Streptomyces lividans	66,269	01-MAY-1995
		GB_BA1:MTCY373	35516	Z73419	Mycobacterium tuberculosis H37Rv complete genome; segment 57/162.	Mycobacterium tuberculosis	65,437	17-Jun-98

TABLE 4: ALIGNMENT RESULTS

		GB_BA1:MLU15186	36241	U15186	Mycobacterium leprae cosmid L471.	Mycobacterium leprae	39,302	09-MAR-1995
rxa01202	1098	GB_BA1:SLATPSYNA	8560	Z22606	S.lividans i protein and ATP synthase genes.	Streptomyces lividans	57,087	01-MAY-1995
		GB_BA1:SLATPSYNA	8560	Z22606	S.lividans i protein and ATP synthase genes.	Streptomyces lividans	38,298	01-MAY-1995
		GB_BA1:MCSQSSHC	5538	Y09978	M.capsulatus orfx, orfy, orfz, sqs and shc genes.	Methylococcus capsulatus	37,626	26-MAY-1998
rxa01204	933	GB_PL1:AP000423	154478	AP000423	Arabidopsis thaliana chloroplast genomic DNA, complete sequence, strain:Columbia.	Chloroplast Arabidopsis thaliana	38,395	15-Sep-99
		GB_HTG6:AC009762	164070	AC009762	Homo sapiens clone RP11-114I16, *** SEQUENCING IN PROGRESS ***, 39 unordered pieces.	Homo sapiens	35,459	04-DEC-1999
		GB_HTG6:AC009762	164070	AC009762	Homo sapiens clone RP11-114I16, *** SEQUENCING IN PROGRESS ***, 39 unordered pieces.	Homo sapiens	36,117	04-DEC-1999
rxa01216	1124	GB_BA1:MTCY10G2	38970	Z92539	Mycobacterium tuberculosis H37Rv complete genome; segment 47/162.	Mycobacterium tuberculosis	39,064	17-Jun-98
		GB_BA2:AF017435	4301	AF017435	Methylobacterium extorquens methanol oxidation genes, glmU-like gene, partial cds, and orfL2, orfL1, orfR genes, complete cds.	Methylobacterium extorquens	42,671	10-MAR-1998
		GB_BA1:CCRFLBDBA	4424	M69228	C.crescentus flagellar gene promoter region.	Caulobacter crescentus	41,054	26-Apr-93
rxa01225	1563	GB_BA2:AF058302	25306	AF058302	Streptomyces roseofulvus frenolicin biosynthetic gene cluster, complete sequence.	Streptomyces roseofulvus	36,205	2-Jun-98
		GB_HTG3:AC007301	165741	AC007301	Drosophila melanogaster chromosome 2 clone BACR04B09 (D576) RPCI-98 04.B.9 map 43E12-44F1 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 150 unordered pieces.	Drosophila melanogaster	39,922	17-Aug-99
		GB_HTG3:AC007301	165741	AC007301	Drosophila melanogaster chromosome 2 clone BACR04B09 (D576) RPCI-98 04.B.9 map 43E12-44F1 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 150 unordered pieces.	Drosophila melanogaster	39,922	17-Aug-99
rxa01227	444	GB_BA1:SERFDXA	3869	M61119	Saccharopolyspora erythraea ferredoxin (fdxA) gene, complete cds.	Saccharopolyspora erythraea	64,908	13-MAR-1996
		GB_BA1:MTV005	37840	AL010186	Mycobacterium tuberculosis H37Rv complete genome; segment 51/162.	Mycobacterium tuberculosis	62,838	17-Jun-98
		GB_BA1:MSGY348	40056	AD000020	Mycobacterium tuberculosis sequence from clone y348.	Mycobacterium tuberculosis	61,712	10-DEC-1996
rxa01242	900	GB_PR3:AC005697	174503	AC005697	Homo sapiens chromosome 17, clone hRPK.138_P_22, complete sequence.	Homo sapiens	35,373	09-OCT-1998
		GB_HTG3:AC010722	160723	AC010722	Homo sapiens clone NH0122L09, *** SEQUENCING IN PROGRESS ***, 2 unordered pieces.	Homo sapiens	39,863	25-Sep-99
		GB_HTG3:AC010722	160723	AC010722	Homo sapiens clone NH0122L09, *** SEQUENCING IN PROGRESS ***, 2 unordered pieces.	Homo sapiens	39,863	25-Sep-99
rxa01243	1083	GB_GSS10:AQ255057	583	AQ255057	mgxb0008N01r CUGI Rice Blast BAC Library Magnaporthe grisea genomic clone mgxb0008N01r, genomic survey sequence.	Magnaporthe grisea	38,722	23-OCT-1998
		GB_IN1:CEK05D4	19000	Z92804	Caenorhabditis elegans cosmid K05D4, complete sequence.	Caenorhabditis elegans	35,448	23-Nov-98
		GB_IN1:CEK05D4	19000	Z92804	Caenorhabditis elegans cosmid K05D4, complete sequence.	Caenorhabditis elegans	35,694	23-Nov-98
rxa01259	981	GB_BA1:CGLPD	1800	Y16642	Corynebacterium glutamicum lpd gene, complete CDS.	Corynebacterium glutamicum	100,000	1-Feb-99
		GB_HTG4:AC010567	143287	AC010567	Drosophila melanogaster chromosome 3L/69C1 clone RPCI98-11N6, *** SEQUENCING IN PROGRESS ***, 70 unordered pieces.	Drosophila melanogaster	37,178	16-OCT-1999
		GB_HTG4:AC010567	143287	AC010567	Drosophila melanogaster chromosome 3L/69C1 clone RPCI98-11N6, ***SEQUENCING IN PROGRESS ***, 70 unordered pieces.	Drosophila melanogaster	37,178	16-OCT-1999
rxa01262	1284	GB_BA2:AF172324	14263	AF172324	Escherichia coli GalF (galF) gene, partial cds; O-antigen repeat unit transporter Wzx (wzx), WbnA (wbnA), O-antigen polymerase Wzy (wzy), WbnB (wbnB), WbnC (wbnC), WbnD (wbnD), WbnE (wbnE), UDP-Glc-4-epimerase GalE (galE), 6-phosphogluconate dehydrogenase Gnd (gnd), UDP-Glc-6-dehydrogenase Ugd (ugd), and WbnF (wbnF) genes, complete cds; and chain length determinant Wzz (wzz) gene, partial cds.	Escherichia coli	59,719	29-OCT-1999

TABLE 4: ALIGNMENT RESULTS

		GB_BA2:ECU78086	4759	U78086	Escherichia coli hypothetical uridine-5'-diphosphoglucose dehydrogenase (ugd) and O-chain length regulator (wzz) genes, complete cds.	Escherichia coli	59,735	5-Nov-97
		GB_BA1:D90841	20226	D90841	E.coli genomic DNA, Kohara clone #351(45.1-45.5 min.).	Escherichia coli	37,904	21-MAR-1997
rxa01311	870	GB_PR3:AC004103	144368	AC004103	Homo sapiens Xp22 BAC GS-619J3 (Genome Systems Human BAC library) complete sequence.	Homo sapiens	37,340	18-Apr-98
		GB_HTG3:AC007383	215529	AC007383	Homo sapiens clone NH0310K15, *** SEQUENCING IN PROGRESS ***, 4 unordered pieces.	Homo sapiens	36,385	25-Sep-99
		GB_HTG3:AC007383	215529	AC007383	Homo sapiens clone NH0310K15, *** SEQUENCING IN PROGRESS ***, 4 unordered pieces.	Homo sapiens	36,385	25-Sep-99
rxa01312	2142	GB_BA2:AE000487	13889	AE000487	Escherichia coli K-12 MG1655 section 377 of 400 of the complete genome.	Escherichia coli	39,494	12-Nov-98
		GB_BA1:MTV016	53662	AL021841	Mycobacterium tuberculosis H37Rv complete genome; segment 143/162.	Mycobacterium tuberculosis	46,252	23-Jun-99
		GB_BA1:U00022	36411	U00022	Mycobacterium leprae cosmid L308.	Mycobacterium leprae	46,368	01-MAR-1994
rxa01325	795	GB_HTG4:AC009245	215767	AC009245	Homo sapiens chromosome 7, *** SEQUENCING IN PROGRESS ***, 24 unordered pieces.	Homo sapiens	36,016	2-Nov-99
		GB_HTG4:AC009245	215767	AC009245	Homo sapiens chromosome 7, *** SEQUENCING IN PROGRESS ***, 24 unordered pieces.	Homo sapiens	36,016	2-Nov-99
		GB_HTG4:AC009245	215767	AC009245	Homo sapiens chromosome 7, *** SEQUENCING IN PROGRESS ***, 24 unordered pieces.	Homo sapiens	39,618	2-Nov-99
rxa01332	576	GB_HTG6:AC007186	225851	AC007186	Drosophila melanogaster chromosome 2 clone BACR03D06 (D569) RPCI-98 03.D.6 map 32A-32A strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 91 unordered pieces.	Drosophila melanogaster	35,366	07-DEC-1999
		GB_HTG6:AC007147	202291	AC007147	Drosophila melanogaster chromosome 2 clone BACR19N18 (D572) RPCI-98 19.N.18 map 32A-32A strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 22 unordered pieces.	Drosophila melanogaster	35,366	07-DEC-1999
		GB_HTG3:AC010207	207890	AC010207	Homo sapiens clone RPCI11-375I20, *** SEQUENCING IN PROGRESS ***, 25 unordered pieces.	Homo sapiens	34,821	16-Sep-99
rxa01350	1107	GB_BA2:AF109682	990	AF109682	Aquaspirillum arcticum malate dehydrogenase (MDH) gene, complete cds.	Aquaspirillum arcticum	58,487	19-OCT-1999
		GB_HTG2:AC006759	103725	AC006759	Caenorhabditis elegans clone Y40G12, *** SEQUENCING IN PROGRESS***, 8 unordered pieces.	Caenorhabditis elegans	37,963	25-Feb-99
		GB_HTG2:AC006759	103725	AC006759	Caenorhabditis elegans clone Y40G12, *** SEQUENCING IN PROGRESS***, 8 unordered pieces.	Caenorhabditis elegans	37,963	25-Feb-99
rxa01365	1497	GB_BA1:MTY20B11	36330	Z95121	Mycobacterium tuberculosis H37Rv complete genome; segment 139/162.	Mycobacterium tuberculosis	38,011	17-Jun-98
		GB_BA1:XANXANAB	3410	M83231	Xanthomonas campestris phosphoglucomutase and phosphomannomutase (xanA) and phosphomannose isomerase and GDP-mannose pyrophosphorylase (xanB) genes, complete cds.	Xanthomonas campestris	47,726	26-Apr-93
		GB_GSS10:AQ194038	697	AQ194038	RPCI11-47D24.TJ RPCI-11 Homo sapiens genomic clone RPCI-11-47D24, genomic survey sequence.	Homo sapiens	36,599	20-Apr-99
rxa01369	1305	GB_BA1:MTY20B11	36330	Z95121	Mycobacterium tuberculosis H37Rv complete genome; segment 139/162.	Mycobacterium tuberculosis	36,940	17-Jun-98
		GB_GSS3:B10037	974	B10037	T27A19-T7 TAMU Arabidopsis thaliana genomic clone T27A19, genomic survey sequence.	Arabidopsis thaliana	35,284	14-MAY-1997
		GB_GSS3:B09549	1097	B09549	T21A19-T7.1 TAMU Arabidopsis thaliana genomic clone T21A19, genomic survey sequence.	Arabidopsis thaliana	38,324	14-MAY-1997
rxa01377	1209	GB_BA1:MTCY71	42729	Z92771	Mycobacterium tuberculosis H37Rv complete genome; segment 141/162.	Mycobacterium tuberculosis	39,778	10-Feb-99
		GB_HTG5:AC007547	262181	AC007547	Homo sapiens clone RP11-252O18, WORKING DRAFT SEQUENCE, 121 unordered pieces.	Homo sapiens	32,658	16-Nov-99

TABLE 4: ALIGNMENT RESULTS

		GB_HTG5:AC007547	262181	AC007547	Homo sapiens clone RP11-252O18, WORKING DRAFT SEQUENCE, 121 unordered pieces.	Homo sapiens	38,395	16-Nov-99
rxa01392	1200	GB_BA2:AF072709	8366	AF072709	Streptomyces lividans amplifiable element AUD4: putative transcriptional regulator, putative ferredoxin, putative cytochrome P450 oxidoreductase, and putative oxidoreductase genes, complete cds; and unknown genes.	Streptomyces lividans	55,221	8-Jul-98
		GB_BA1:CGLYSEG	2374	X96471	C.glutamicum lysE and lysG genes.	Corynebacterium glutamicum	100,000	24-Feb-97
		GB_PR4:AC005906	185952	AC005906	Homo sapiens 12p13.3 BAC RPCI11-429A20 (Roswell Park Cancer Institute Human BAC Library) complete sequence.	Homo sapiens	36,756	30-Jan-99
rxa01436	1314	GB_BA1:CGPTAACKA	3657	X89084	C.glutamicum pta gene and ackA gene.	Corynebacterium glutamicum	100,000	23-MAR-1999
		GB_BA1:D90861	14839	D90861	E.coli genomic DNA, Kohara clone #405(52.0-52.3 min.).	Escherichia coli	53,041	29-MAY-1997
		GB_PAT:E02087	1200	E02087	DNA encoding acetate kinase protein form Escherichia coli.	Escherichia coli	54,461	29-Sep-97
rxa01468	948	GB_GSS1:HPU60627	280	U60627	Helicobacter pylori feoB-like DNA sequence, genomic survey sequence.	Helicobacter pylori	39,286	9-Apr-97
		GB_EST31:AI701691	349	AI701691	we81c04.x1 Soares_NFL_T_GBC_S1 Homo sapiens cDNA clone IMAGE:2347494 3' similar to gb:L19686_rna1 MACROPHAGE MIGRATION INHIBITORY FACTOR (HUMAN);, mRNA sequence.	Homo sapiens	39,412	3-Jun-99
		GB_EST15:AA480256	389	AA480256	ne31f04.s1 NCI_CGAP_Co3 Homo sapiens cDNA clone IMAGE:898975 3' similar to gb:L19686_rna1 MACROPHAGE MIGRATION INHIBITORY FACTOR (HUMAN);, mRNA sequence.	Homo sapiens	39,574	14-Aug-97
rxa01478	1959	GB_BA1:SCI51	40745	AL109848	Streptomyces coelicolor cosmid I51.	Streptomyces coelicolor A3(2)	54,141	16-Aug-99
		GB_BA1:SCE36	12581	AL049763	Streptomyces coelicolor cosmid E36.	Streptomyces coelicolor	38,126	05-MAY-1999
		GB_BA1:CGU43535	2531	U43535	Corynebacterium glutamicum multidrug resistance protein (cmr) gene, complete cds.	Corynebacterium glutamicum	41,852	9-Apr-97
rxa01482	1998	GB_BA1:SC6G4	41055	AL031317	Streptomyces coelicolor cosmid 6G4.	Streptomyces coelicolor	62,149	20-Aug-98
		GB_BA1:U00020	36947	U00020	Mycobacterium leprae cosmid B229.	Mycobacterium leprae	38,303	01-MAR-1994
		GB_BA1:MTCY77	22255	Z95389	Mycobacterium tuberculosis H37Rv complete genome; segment 146/162.	Mycobacterium tuberculosis	38,179	18-Jun-98
rxa01534								
rxa01535	1530	GB_BA1:MLCB1222	34714	AL049491	Mycobacterium leprae cosmid B1222.	Mycobacterium leprae	66,208	27-Aug-99
		GB_BA1:MTV017	67200	AL021897	Mycobacterium tuberculosis H37Rv complete genome; segment 48/162.	Mycobacterium tuberculosis	38,553	24-Jun-99
		GB_BA1:PAU72494	4368	U72494	Pseudomonas aeruginosa fumarase (fumC) and Mn superoxide dismutase (sodA) genes, complete cds.	Pseudomonas aeruginosa	52,690	23-OCT-1996
rxa01550	1635	GB_BA1:D90907	132419	D90907	Synechocystis sp. PCC6803 complete genome, 9/27, 1056467-1188885.	Synechocystis sp.	56,487	7-Feb-99
		GB_IN2:AF073177	9534	AF073177	Drosophila melanogaster glycogen phosphorylase (GlyP) gene, complete cds.	Drosophila melanogaster	55,100	1-Jul-99
		GB_IN2:AF073179	3159	AF073179	Drosophila melanogaster glycogen phosphorylase (Glp1) mRNA, complete cds.	Drosophila melanogaster	56,708	27-Apr-99
rxa01562								
rxa01569	1482	GB_BA1:D78182	7836	D78182	Streptococcus mutans DNA for dTDP-rhamnose synthesis pathway, complete cds.	Streptococcus mutans	44,050	5-Feb-99
		GB_BA2:AF079139	4342	AF079139	Streptomyces venezuelae pikCD operon, complete sequence.	Streptomyces venezuelae	38,587	28-OCT-1998
		GB_BA2:AF087022	1470	AF087022	Streptomyces venezuelae cytochrome P450 monooxygenase (picK) gene, complete cds.	Streptomyces venezuelae	38,621	15-OCT-1998
rxa01570	978	GB_BA1:MTCY63	38900	Z96800	Mycobacterium tuberculosis H37Rv complete genome; segment 16/162.	Mycobacterium tuberculosis	59,035	17-Jun-98

TABLE 4: ALIGNMENT RESULTS

		GB_BA2:AF097519	4594	AF097519	Klebsiella pneumoniae dTDP-D-glucose 4,6 dehydratase (rmlB), glucose-1-phosphate thymidylyl transferase (rmlA), dTDP-4-keto-L-rhamnose reductase (rmlD), dTDP-4-keto-6-deoxy-D-glucose 3,5-epimerase (rmlC), and rhamnosyl transferase (wbbL) genes, complete cds.	Klebsiella pneumoniae	59,714	4-Nov-98
		GB_BA2:NGOCPSPS	8905	L09189	Neisseria meningitidis dTDP-D-glucose 4,6-dehydratase (rfbB), glucose-1-phosphate thymidyl transferase (rfbA) and rfbC genes, complete cds and UPD-glucose-4-epimerase (galE) pseudogene.	Neisseria meningitidis	58,384	30-Jul-96
rxa01571	723	GB_BA1:AB011413	12070	AB011413	Streptomyces griseus genes for Orf2, Orf3, Orf4, Orf5, AfsA, Orf8, partial and complete cds.	Streptomyces griseus	57,500	7-Aug-98
		GB_BA1:AB011413	12070	AB011413	Streptomyces griseus genes for Orf2, Orf3, Orf4, Orf5, AfsA, Orf8, partial and complete cds.	Streptomyces griseus	35,655	7-Aug-98
rxa01572	615	GB_BA1:AB011413	12070	AB011413	Streptomyces griseus genes for Orf2, Orf3, Orf4, Orf5, AfsA, Orf8, partial and complete cds.	Streptomyces griseus	57,843	7-Aug-98
		GB_BA1:AB011413	12070	AB011413	Streptomyces griseus genes for Orf2, Orf3, Orf4, Orf5, AfsA, Orf8, partial and complete cds.	Streptomyces griseus	38,119	7-Aug-98
rxa01606	2799	GB_VI:CFU72240	4783	U72240	Choristoneura fumiferana nuclear polyhedrosis virus ETM protein homolog, 79 kDa protein homolog, 15 kDa protein homolog and GTA protein homolog genes, complete cds.	Choristoneura fumiferana nucleopolyhedrovirus	37,115	29-Jan-99
		GB_GSS10:AQ213248	408	AQ213248	HS_3249_B1_A02_MR CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=3249 Col=3 Row=B, genomic survey sequence.	Homo sapiens	34,559	18-Sep-98
		GB_GSS8:AQ070145	285	AQ070145	HS_3027_B1_H02_MR CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=3027 Col=3 Row=P, genomic survey sequence.	Homo sapiens	40,351	5-Aug-98
rxa01626	468	GB_PR4:AF152510	2490	AF152510	Homo sapiens protocadherin gamma A3 short form protein (PCDH-gamma-A3) variable region sequence, complete cds.	Homo sapiens	34,298	14-Jul-99
		GB_PR4:AF152323	4605	AF152323	Homo sapiens protocadherin gamma A3 (PCDH-gamma-A3) mRNA, complete cds.	Homo sapiens	34,298	22-Jul-99
		GB_PR4:AF152509	2712	AF152509	Homo sapiens PCDH-gamma-A3 gene, aberrantly spliced, mRNA sequence.	Homo sapiens	34,298	14-Jul-99
rxa01632	1128	GB_HTG4:AC006590	127171	AC006590	Drosophila melanogaster chromosome 2 clone BACR13N02 (D543) RPCI-98 13.N.2 map 36E-36E strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 101 unordered pieces.	Drosophila melanogaster	33,812	19-OCT-1999
		GB_HTG4:AC006590	127171	AC006590	Drosophila melanogaster chromosome 2 clone BACR13N02 (D543) RPCI-98 13.N.2 map 36E-36E strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 101 unordered pieces.	Drosophila melanogaster	33,812	19-OCT-1999
		GB_GSS8:B99182	415	B99182	CIT-HSP-2280I13.TR CIT-HSP Homo sapiens genomic clone 2280I13, genomic survey sequence.	Homo sapiens	36,111	26-Jun-98
rxa01633	1206	GB_BA1:BSUB0009	208780	Z99112	Bacillus subtilis complete genome (section 9 of 21): from 1598421 to 1807200.	Bacillus subtilis	36,591	26-Nov-97
		GB_BA1:BSUB0009	208780	Z99112	Bacillus subtilis complete genome (section 9 of 21): from 1598421 to 1807200.	Bacillus subtilis	34,941	26-Nov-97
		GB_HTG2:AC006247	174368	AC006247	Drosophila melanogaster chromosome 2 clone BACR48I10 (D505) RPCI-98 48.I.10 map 49E6-49F8 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 17 unordered pieces.	Drosophila melanogaster	37,037	2-Aug-99
rxa01695	1623	GB_BA1:CGA224946	2408	AJ224946	Corynebacterium glutamicum DNA for L-Malate:quinone oxidoreductase.	Corynebacterium glutamicum	100,000	11-Aug-98
		GB_BA1:MTCY24A1	20270	Z95207	Mycobacterium tuberculosis H37Rv complete genome; segment 124/162.	Mycobacterium tuberculosis	38,626	17-Jun-98
		GB_IN1:DMU15974	2994	U15974	Drosophila melanogaster kinesin-like protein (klp68d) mRNA, complete cds.	Drosophila melanogaster	36,783	18-Jul-95

TABLE 4: ALIGNMENT RESULTS

rxa01702	1155	GB_BA1:CGFDA	3371	X17313	Corynebacterium glutamicum fda gene for fructose-bisphosphate aldolase (EC 4.1.2.13).	Corynebacterium glutamicum	99,913	12-Sep-93
		GB_BA1:MTY13E10	35019	Z95324	Mycobacterium tuberculosis H37Rv complete genome; segment 18/162.	Mycobacterium tuberculosis	38,786	17-Jun-98
		GB_BA1:MLCB4	36310	AL023514	Mycobacterium leprae cosmid B4.	Mycobacterium leprae	38,238	27-Aug-99
rxa01743	901	GB_IN2:CELC27H5	35840	U14635	Caenorhabditis elegans cosmid C27H5.	Caenorhabditis elegans	35,334	13-Jul-95
		GB_EST24:AI167112	579	AI167112	xylem.est.878 Poplar xylem Lambda ZAPII library Populus balsamifera subsp. trichocarpa cDNA 5', mRNA sequence.	Populus balsamifera subsp. trichocarpa	39,222	03-DEC-1998
		GB_GSS9:AQ102635	347	AQ102635	HS_3048_B1_F08_MF CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=3048 Col=15 Row=L, genomic survey sequence.	Homo sapiens	40,653	27-Aug-98
rxa01744	1662	GB_BA1:MTCY01B2	35938	Z95554	Mycobacterium tuberculosis H37Rv complete genome; segment 72/162.	Mycobacterium tuberculosis	36,650	17-Jun-98
		GB_GSS1:AF009226	665	AF009226	Mycobacterium tuberculosis cytochrome D oxidase subunit I (appC) gene, partial sequence, genomic survey sequence.	Mycobacterium tuberculosis	63,438	31-Jul-97
		GB_BA1:SCD78	36224	AL034355	Streptomyces coelicolor cosmid D78.	Streptomyces coelicolor	53,088	26-Nov-98
rxa01745	836	GB_BA1:MTCY190	34150	Z70283	Mycobacterium tuberculosis H37Rv complete genome; segment 98/162.	Mycobacterium tuberculosis	62,081	17-Jun-98
		GB_BA1:MLCB22	40281	Z98741	Mycobacterium leprae cosmid B22.	Mycobacterium leprae	61,364	22-Aug-97
		GB_BA2:AE000175	15067	AE000175	Escherichia coli K-12 MG1655 section 65 of 400 of the complete genome.	Escherichia coli	52,323	12-Nov-98
rxa01758	1140	GB_PR3:HS57G9	113872	Z95116	Human DNA sequence from BAC 57G9 on chromosome 22q12.1 Contains ESTs, CA repeat, GSS.	Homo sapiens	39,209	23-Nov-99
		GB_PL2:YSCH9666	39057	U10397	Saccharomyces cerevisiae chromosome VIII cosmid 9666.	Saccharomyces cerevisiae	40,021	5-Sep-97
		GB_PL2:YSCH9986	41664	U00027	Saccharomyces cerevisiae chromosome VIII cosmid 9986.	Saccharomyces cerevisiae	34,375	29-Aug-97
rxa01814	1785	GB_BA1:ABCCELB	2058	L24077	Acetobacter xylinum phosphoglucomutase (celB) gene, complete cds.	Acetobacter xylinus	62,173	21-Sep-94
		GB_BA1:MTCY22D7	31859	Z83866	Mycobacterium tuberculosis H37Rv complete genome; segment 133/162.	Mycobacterium tuberculosis	39,749	17-Jun-98
		GB_BA1:MTCY22D7	31859	Z83866	Mycobacterium tuberculosis H37Rv complete genome; segment 133/162.	Mycobacterium tuberculosis	40,034	17-Jun-98
rxa01851	1809	GB_GSS9:AQ142579	529	AQ142579	HS_2222_B1_H03_MR CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=2222 Col=5 Row=P, genomic survey sequence.	Homo sapiens	38,068	24-Sep-98
		GB_IN2:AC005889	108924	AC005889	Drosophila melanogaster, chromosome 2L, region 30A3- 30A6, P1 clones DS06958 and DS03097, complete sequence.	Drosophila melanogaster	36,557	30-OCT-1998
		GB_GSS1:AG008814	637	AG008814	Homo sapiens genomic DNA, 21q region, clone: B137B7BB68, genomic survey sequence.	Homo sapiens	35,316	7-Feb-99
rxa01859	1050	GB_BA2:AF183408	63626	AF183408	Microcystis aeruginosa DNA polymerase III beta subunit (dnaN) gene, partial cds; microcystin synthetase gene cluster, complete sequence; Uma1 (uma1), Uma2 (uma2), Uma3 (uma3), Uma4 (uma4), and Uma5 (uma5) genes, complete cds; and Uma6 (uma6) gene, partial cds.	Microcystis aeruginosa	36,364	03-OCT-1999
		GB_HTG5:AC008031	158889	AC008031	Trypanosoma brucei chromosome II clone RPCI93-25N14, *** SEQUENCING IN PROGRESS ***, 2 unordered pieces.	Trypanosoma brucei	35,334	15-Nov-99
		GB_BA2:AF183408	63626	AF183408	Microcystis aeruginosa DNA polymerase III beta subunit (dnaN) gene, partial cds; microcystin synthetase gene cluster, complete sequence; Uma1 (uma1), Uma2 (uma2), Uma3 (uma3), Uma4 (uma4), and Uma5 (uma5) genes, complete cds; and Uma6 (uma6) gene, partial cds.	Microcystis aeruginosa	36,529	03-OCT-1999
rxa01865	438	GB_BA1:SERFDXA	3869	M61119	Saccharopolyspora erythraea ferredoxin (fdxA) gene, complete cds.	Saccharopolyspora erythraea	59,862	13-MAR-1996
		GB_BA1:MTV005	37840	AL010186	Mycobacterium tuberculosis H37Rv complete genome; segment 51/162.	Mycobacterium tuberculosis	61,949	17-Jun-98
		GB_BA1:MSGY348	40056	AD000020	Mycobacterium tuberculosis sequence from clone y348.	Mycobacterium tuberculosis	59,908	10-DEC-1996
rxa01882	1113	GB_PR1:HUMADRA2C	1491	J03853	Human kidney alpha-2-adrenergic receptor mRNA, complete cds.	Homo sapiens	36,899	27-Apr-93
		GB_PR4:HSU72648	4850	U72648	Homo sapiens alpha2-C4-adrenergic receptor gene, complete cds.	Homo sapiens	36,899	23-Nov-98

TABLE 4: ALIGNMENT RESULTS

		GB_GSS3:B42200	387	B42200	HS-1055-B1-A03-MR.abi CIT Human Genomic Sperm Library C Homo sapiens genomic clone Plate=CT 777 Col=5 Row=B, genomic survey sequence.	Homo sapiens	34,805	18-OCT-1997
rxa01884	1913	GB_BA1:MTCY48	35377	Z74020	Mycobacterium tuberculosis H37Rv complete genome; segment 69/162.	Mycobacterium tuberculosis	37,892	17-Jun-98
		GB_BA1:SCO001206	9184	AJ001206	Streptomyces coelicolor A3(2), glycogen metabolism cluster II.	Streptomyces coelicolor	40,413	29-MAR-1999
		GB_BA1:D90908	122349	D90908	Synechocystis sp. PCC6803 complete genome, 10/27, 1188886-1311234.	Synechocystis sp.	47,792	7-Feb-99
rxa01886	897	GB_GSS9:AQ116291	572	AQ116291	RPCI11-49P6.TK.1 RPCI-11 Homo sapiens genomic clone RPCI-11-49P6, genomic survey sequence.	Homo sapiens	43,231	20-Apr-99
		GB_BA2:AE001721	17632	AE001721	Thermotoga maritima section 33 of 136 of the complete genome.	Thermotoga maritima	39,306	2-Jun-99
		GB_EST16:AA567090	596	AA567090	GM01044.5prime GM Drosophila melanogaster ovary BlueScript Drosophila melanogaster cDNA clone GM01044 5prime, mRNA sequence.	Drosophila melanogaster	42,807	28-Nov-98
rxa01887	1134	GB_HTG6:AC008147	303147	AC008147	Homo sapiens clone RP3-405J10, *** SEQUENCING IN PROGRESS ***, 102 unordered pieces.	Homo sapiens	36,417	03-DEC-1999
		GB_HTG6:AC008147	303147	AC008147	Homo sapiens clone RP3-405J10, *** SEQUENCING IN PROGRESS ***, 102 unordered pieces.	Homo sapiens	37,667	03-DEC-1999
		GB_BA2:ALW243431	26953	AJ243431	Acinetobacter lwoffii wzc, wzb, wza, weeA, weeB, wceC, wzx, wzy, weeD, weeE, weeF, weeG, weeH, weeI, weeJ, weeK, galU, ugd, pgi, galE, pgm (partial) and mip (partial) genes (emulsan biosynthetic gene cluster), strain RAG-1.	Acinetobacter lwoffii	39,640	01-OCT-1999
rxa01888	658	GB_HTG2:AC008197	125235	AC008197	Drosophila melanogaster chromosome 3 clone BACR02L12 (D753) RPCI-98 02.L.12 map 94B-94C strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 113 unordered pieces.	Drosophila melanogaster	32,969	2-Aug-99
		GB_HTG2:AC008197	125235	AC008197	Drosophila melanogaster chromosome 3 clone BACR02L12 (D753) RPCI-98 02.L.12 map 94B-94C strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 113 unordered pieces.	Drosophila melanogaster	32,969	2-Aug-99
		GB_EST36:AI881527	598	AI881527	606070C09.y1 606 - Ear tissue cDNA library from Schmidt lab Zea mays cDNA, mRNA sequence.	Zea mays	43,617	21-Jul-99
rxa01891	887	GB_VI:HIV232971	621	AJ232971	Human immunodeficiency virus type 1 subtype C nef gene, patient MP83.	Human immunodeficiency virus type 1	40,040	05-MAR-1999
		GB_PL1:AFCHSE	6158	Y09542	A.fumigatus chsE gene.	Aspergillus fumigatus	37,844	1-Apr-97
		GB_PR3:AF064858	193387	AF064858	Homo sapiens chromosome 21q22.3 BAC 28F9, complete sequence.	Homo sapiens	37,136	2-Jun-98
rxa01895	1051	GB_BA1:CGL238250	1593	AJ238250	Corynebacterium glutamicum ndh gene.	Corynebacterium glutamicum	100,000	24-Apr-99
		GB_BA2:AF038423	1376	AF038423	Mycobacterium smegmatis NADH dehydrogenase (ndh) gene, complete cds.	Mycobacterium smegmatis	65,254	05-MAY-1998
		GB_BA1:MTCY359	36021	Z83859	Mycobacterium tuberculosis H37Rv complete genome; segment 84/162.	Mycobacterium tuberculosis	40,058	17-Jun-98
rxa01901	1383	GB_BA1:MSGB38COS	37114	L01095	M. leprae genomic DNA sequence, cosmid B38 bfr gene, complete cds.	Mycobacterium leprae	59,551	6-Sep-94
		GB_BA1:SCE63	37200	AL035640	Streptomyces coelicolor cosmid E63.	Streptomyces coelicolor	39,468	17-MAR-1999
		GB_PR3:AF093117	147216	AF093117	Homo sapiens chromosome 7qtelo BAC E3, complete sequence.	Homo sapiens	39,291	02-OCT-1998
rxa01927	1503	GB_BA1:CGPAN	2164	X96580	C.glutamicum panB, panC & xylB genes.	Corynebacterium glutamicum	38,384	11-MAY-1999
		GB_BA1:ASXYLA	1905	X59466	Arthrobacter Sp. N.R.R.L. B3728 xylA gene for D-xylose(D-glucose) isomerase.	Arthrobacter sp.	56,283	04-MAY-1992
		GB_HTG3:AC009500	176060	AC009500	Homo sapiens clone NH0511A20, *** SEQUENCING IN PROGRESS ***, 6 unordered pieces.	Homo sapiens	37,593	24-Aug-99
rxa01952	1836	GB_BA2:AE000739	13335	AE000739	Aquifex aeolicus section 71 of 109 of the complete genome.	Aquifex aeolicus	36,309	25-MAR-1998
		GB_EST28:AI519629	612	AI519629	LD39282.5prime LD Drosophila melanogaster embryo pOT2 Drosophila melanogaster cDNA clone LD39282 5prime, mRNA sequence.	Drosophila melanogaster	41,941	16-MAR-1999
		GB_EST21:AA949396	767	AA949396	LD28277.5prime LD Drosophila melanogaster embryo pOT2 Drosophila melanogaster cDNA clone LD28277 5prime, mRNA sequence.	Drosophila melanogaster	39,855	25-Nov-98

TABLE 4: ALIGNMENT RESULTS

rxa01989	630	GB_BA1:BSPGIA	1822	X16639	Bacillus stearothermophilus pgiA gene for phosphoglucoisomerase isoenzyme A (EC 5.3.1.9).	Bacillus stearothermophilus	66,292	20-Apr-95
		GB_BA1:BSUB0017	217420	Z99120	Bacillus subtilis complete genome (section 17 of 21): from 3197001 to 3414420.	Bacillus subtilis	37,255	26-Nov-97
		GB_BA2:AF132127	8452	AF132127	Streptococcus mutans sorbitol phosphoenolpyruvate:sugar phosphotransferase operon, complete sequence and unknown gene.	Streptococcus mutans	63,607	28-Sep-99
rxa02026	720	GB_BA1:SXSCRBA	3161	X67744	S.xylosus scrB and scrR genes.	Staphylococcus xylosus	67,778	28-Nov-96
		GB_BA1:BSUB0020	212150	Z99123	Bacillus subtilis complete genome (section 20 of 21): from 3798401 to 4010550.	Bacillus subtilis	35,574	26-Nov-97
		GB_BA1:BSGENR	97015	X73124	B.subtilis genomic region (325 to 333).	Bacillus subtilis	51,826	2-Nov-93
rxa02028	526	GB_BA1:MTCI237	27030	Z94752	Mycobacterium tuberculosis H37Rv complete genome; segment 46/162.	Mycobacterium tuberculosis	54,476	17-Jun-98
		GB_PL2:SCE9537	66030	U18778	Saccharomyces cerevisiae chromosome V cosmids 9537, 9581, 9495, 9867, and lambda clone 5898.	Saccharomyces cerevisiae	36,100	1-Aug-97
		GB_GSS13:AQ501177	767	AQ501177	V26G9 mTn-3xHA/lacZ Insertion Library Saccharomyces cerevisiae genomic 5', genomic survey sequence.	Saccharomyces cerevisiae	32,039	29-Apr-99
rxa02054	1140	GB_BA1:MLCB1222	34714	AL049491	Mycobacterium leprae cosmid B1222.	Mycobacterium leprae	61,896	27-Aug-99
		GB_BA1:MTY13E12	43401	Z95390	Mycobacterium tuberculosis H37Rv complete genome; segment 147/162.	Mycobacterium tuberculosis	59,964	17-Jun-98
		GB_BA1:MTU43540	3453	U43540	Mycobacterium tuberculosis rfbA, rhamnose biosynthesis protein (rfbA), and rmlC genes, complete cds.	Mycobacterium tuberculosis	59,659	14-Aug-97
rxa02056	2891	GB_PAT:E14601	4394	E14601	Brevibacterium lactofermentum gene for alpha-ketoglutaric acid dehydrogenase.	Corynebacterium glutamicum	98,928	28-Jul-99
		GB_BA1:D84102	4394	D84102	Corynebacterium glutamicum DNA for 2-oxoglutarate dehydrogenase, complete cds.	Corynebacterium glutamicum	98,928	6-Feb-99
		GB_BA1:MTV006	22440	AL021006	Mycobacterium tuberculosis H37Rv complete genome; segment 54/162.	Mycobacterium tuberculosis	39,265	18-Jun-98
rxa02061	1617	GB_HTG7:AC005883	211682	AC005883	Homo sapiens chromosome 17 clone RP11-958E11 map 17, *** SEQUENCING IN PROGRESS ***, 2 ordered pieces.	Homo sapiens	37,453	08-DEC-1999
		GB_PL2:ATAC003033	84254	AC003033	Arabidopsis thaliana chromosome II BAC T21L14 genomic sequence, complete sequence.	Arabidopsis thaliana	37,711	19-DEC-1997
		GB_PL2:ATAC002334	75050	AC002334	Arabidopsis thaliana chromosome II BAC F25I18 genomic sequence, complete sequence.	Arabidopsis thaliana	37,711	04-MAR-1998
rxa02063	1350	GB_BA1:SCGLGC	1518	X89733	S.coelicolor DNA for glgC gene.	Streptomyces coelicolor	56,972	12-Jul-99
		GB_GSS4:AQ687350	786	AQ687350	nbxb0074H11r CUGI Rice BAC Library Oryza sativa genomic clone nbxb0074H11r, genomic survey sequence.	Oryza sativa	40,696	1-Jul-99
		GB_EST38:AW028530	444	AW028530	wv27f10.x1 NCI_CGAP_Kid11 Homo sapiens cDNA clone IMAGE:2530795 3' similar to WP:T03G11.6 CE04874 ;, mRNA sequence.	Homo sapiens	36,795	27-OCT-1999
rxa02100	2348	GB_BA1:MSGY151	37036	AD000018	Mycobacterium tuberculosis sequence from clone y151.	Mycobacterium tuberculosis	40,156	10-DEC-1996
		GB_BA1:MTCY130	32514	Z73902	Mycobacterium tuberculosis H37Rv complete genome; segment 59/162.	Mycobacterium tuberculosis	55,218	17-Jun-98
		GB_BA1:SCO001205	9589	AJ001205	Streptomyces coelicolor A3(2) glycogen metabolism clusterI.	Streptomyces coelicolor	38,475	29-MAR-1999
rxa02122	822	GB_BA1:D90858	13548	D90858	E.coli genomic DNA, Kohara clone #401(51.3-51.6 min.).	Escherichia coli	38,586	29-MAY-1997
		GB_EST37:AI948595	469	AI948595	wq07d12.x1 NCI_CGAP_Kid12 Homo sapiens cDNA clone IMAGE:2470583 3', mRNA sequence.	Homo sapiens	37,259	6-Sep-99
		GB_HTG3:AC010387	220665	AC010387	Homo sapiens chromosome 5 clone CITB-H1_2074D8, *** SEQUENCING IN PROGRESS ***, 77 unordered pieces.	Homo sapiens	38,868	15-Sep-99
rxa02140	1200	GB_BA1:MSGB1551CS	36548	L78813	Mycobacterium leprae cosmid B1551 DNA sequence.	Mycobacterium leprae	51,399	15-Jun-96
		GB_BA1:MSGB1554CS	36548	L78814	Mycobacterium leprae cosmid B1554 DNA sequence.	Mycobacterium leprae	51,399	15-Jun-96
		GB_RO:AF093099	2482	AF093099	Mus musculus transcription factor TBLYM (Tblym) mRNA, complete cds.	Mus musculus	36,683	01-OCT-1999
rxa02142	774	GB_BA1:MTCY190	34150	Z70283	Mycobacterium tuberculosis H37Rv complete genome; segment 98/162.	Mycobacterium tuberculosis	57,292	17-Jun-98
		GB_BA1:SC6G10	36734	AL049497	Streptomyces coelicolor cosmid 6G10.	Streptomyces coelicolor	35,058	24-MAR-1999

TABLE 4: ALIGNMENT RESULTS

		GB_BA1:AB016787	5550	AB016787	Pseudomonas putida genes for cytochrome o ubiquinol oxidase A-E and 2 ORFs, complete cds.	Pseudomonas putida	47,403	5-Aug-99
rxa02143	1011	GB_BA1:MTCY190	34150	Z70283	Mycobacterium tuberculosis H37Rv complete genome; segment 98/162.	Mycobacterium tuberculosis	57,317	17-Jun-98
		GB_BA1:MSGB1551CS	36548	L78813	Mycobacterium leprae cosmid B1551 DNA sequence.	Mycobacterium leprae	38,159	15-Jun-96
		GB_BA1:MSGB1554CS	36548	L78814	Mycobacterium leprae cosmid B1554 DNA sequence.	Mycobacterium leprae	38,159	15-Jun-96
rxa02144	1347	GB_BA1:MTCY190	34150	Z70283	Mycobacterium tuberculosis H37Rv complete genome; segment 98/162.	Mycobacterium tuberculosis	55,530	17-Jun-98
		GB_HTG3:AC011500_0	300851	AC011500	Homo sapiens chromosome 19 clone CIT978SKB_60E11, *** SEQUENCING IN PROGRESS ***, 246 unordered pieces.	Homo sapiens	39,659	18-Feb-00
		GB_HTG3:AC011500_0	300851	AC011500	Homo sapiens chromosome 19 clone CIT978SKB_60E11, *** SEQUENCING IN PROGRESS ***, 246 unordered pieces.	Homo sapiens	39,659	18-Feb-00
rxa02147	1140	GB_EST28:AI492095	485	AI492095	tg07a01.x1 NCI_CGAP_CLL1 Homo sapiens cDNA clone IMAGE:2108040 3', mRNA sequence.	Homo sapiens	39,798	30-MAR-1999
		GB_EST10:AA157467	376	AA157467	zo50e01.r1 Stratagene endothelial cell 937223 Homo sapiens cDNA clone IMAGE:590328 5', mRNA sequence.	Homo sapiens	36,436	11-DEC-1996
		GB_EST10:AA157467	376	AA157467	zo50e01.r1 Stratagene endothelial cell 937223 Homo sapiens cDNA clone IMAGE:590328 5', mRNA sequence.	Homo sapiens	36,436	11-DEC-1996
rxa02149	1092	GB_PR3:HSBK277P6	61698	AL117347	Human DNA sequence from clone 277P6 on chromosome 1q25.3-31.2, complete sequence.	Homo sapiens	36,872	23-Nov-99
		GB_BA2:EMB065R075	360	AF116423	Rhizobium etli mutant MB045 RosR-transcriptionally regulated sequence.	Rhizobium etli	43,175	06-DEC-1999
		GB_EST34:AI789323	574	AI789323	uk53g05.y1 Sugano mouse kidney mkia Mus musculus cDNA clone IMAGE:1972760 5' similar to WP:K11H12.8 CE12160 ;, mRNA sequence.	Mus musculus	39,715	2-Jul-99
rxa02175	1416	GB_BA1:CGGLTG	3013	X66112	C.glutamicum glt gene for citrate synthase and ORF.	Corynebacterium glutamicum	100,000	17-Feb-95
		GB_BA1:MTCY31	37630	Z73101	Mycobacterium tuberculosis H37Rv complete genome; segment 41/162.	Mycobacterium tuberculosis	64,331	17-Jun-98
		GB_BA1:MLCB57	38029	Z99494	Mycobacterium leprae cosmid B57.	Mycobacterium leprae	62,491	10-Feb-99
rxa02196	816	GB_RO:RATDAPRP	2819	M76426	Rattus norvegicus dipeptidyl aminopeptidase-related protein (dpp6) mRNA, complete cds.	Rattus norvegicus	38,791	31-MAY-1995
		GB_GSS8:AQ012162	763	AQ012162	127PB037070197 Cosmid library of chromosome II Rhodobacter sphaeroides genomic clone 127PB037070197, genomic survey sequence.	Rhodobacter sphaeroides	40,044	4-Jun-98
		GB_RO:RATDAPRP	2819	M76426	Rattus norvegicus dipeptidyl aminopeptidase-related protein (dpp6) mRNA, complete cds.	Rattus norvegicus	37,312	31-MAY-1995
rxa02209	1694	GB_BA1:AB025424	2995	AB025424	Corynebacterium glutamicum gene for aconitase, partial cds.	Corynebacterium glutamicum	99,173	3-Apr-99
		GB_BA2:AF002133	15437	AF002133	Mycobacterium avium strain GIR10 transcriptional regulator (mav81) gene, partial cds, aconitase (acn), invasin 1 (inv1), invasin 2 (inv2), transcriptional regulator (moxR), ketoacyl-reductase (fabG), enoyl-reductase (inhA) and ferrochelatase (mav272) genes, complete cds.	Mycobacterium avium	40,219	26-MAR-1998
		GB_BA1:MTV007	32806	AL021184	Mycobacterium tuberculosis H37Rv complete genome; segment 64/162.	Mycobacterium tuberculosis	38,253	17-Jun-98
rxa02213	874	GB_BA1:AB025424	2995	AB025424	Corynebacterium glutamicum gene for aconitase, partial cds.	Corynebacterium glutamicum	99,096	3-Apr-99
		GB_BA1:MTV007	32806	AL021184	Mycobacterium tuberculosis H37Rv complete genome; segment 64/162.	Mycobacterium tuberculosis	34,937	17-Jun-98
		GB_BA2:AF002133	15437	AF002133	Mycobacterium avium strain GIR10 transcriptional regulator (mav81) gene, partial cds, aconitase (acn), invasin 1 (inv1), invasin 2 (inv2), transcriptional regulator (moxR), ketoacyl-reductase (fabG), enoyl-reductase (inhA) and ferrochelatase (mav272) genes, complete cds.	Mycobacterium avium	36,885	26-MAR-1998

TABLE 4: ALIGNMENT RESULTS

rxa02245	780	GB_BA2:RCU23145	5960	U23145	Rhodobacter capsulatus Calvin cycle carbon dioxide fixation operon: fructose-1,6-/sedoheptulose-1,7-bisphosphate aldolase (cbbA) gene, partial cds, Form II ribulose-1,5-bisphosphate carboxylase/oxygenase (cbbM) gene, complete cds, and Calvin cycle operon: pentose-5-phosphate-3-epimerase (cbbE), phosphoglycolate phosphatase (cbbZ), and cbbY genes, complete cds.	Rhodobacter capsulatus	48,701	28-OCT-1997
		GB_BA1:ECU82664	139818	U82664	Escherichia coli minutes 9 to 11 genomic sequence.	Escherichia coli	39,119	11-Jan-97
		GB_HTG2:AC007922	158858	AC007922	Homo sapiens chromosome 18 clone hRPK.178_F_10 map 18, *** SEQUENCING IN PROGRESS ***, 11 unordered pieces.	Homo sapiens	33,118	26-Jun-99
rxa02256	1125	GB_BA1:CGGAPPGK	3804	X59403	C.glutamicum gap, pgk and tpi genes for glyceraldehyde-3-phosphate, phosphoglycerate kinase and triosephosphate isomerase.	Corynebacterium glutamicum	99,289	05-OCT-1992
		GB_BA1:SCC54	30753	AL035591	Streptomyces coelicolor cosmid C54.	Streptomyces coelicolor	36,951	11-Jun-99
		GB_BA1:MTCY493	40790	Z95844	Mycobacterium tuberculosis H37Rv complete genome; segment 63/162.	Mycobacterium tuberculosis	64,196	19-Jun-98
rxa02257	1338	GB_BA1:CGGAPPGK	3804	X59403	C.glutamicum gap, pgk and tpi genes for glyceraldehyde-3-phosphate, phosphoglycerate kinase and triosephosphate isomerase.	Corynebacterium glutamicum	98,873	05-OCT-1992
		GB_BA1:MTCY493	40790	Z95844	Mycobacterium tuberculosis H37Rv complete genome; segment 63/162.	Mycobacterium tuberculosis	61,273	19-Jun-98
		GB_BA2:MAU82749	2530	U82749	Mycobacterium avium glyceraldehyde-3-phosphate dehydrogenase homolog (gapdh) gene, complete cds; and phosphoglycerate kinase gene, partial cds.	Mycobacterium avium	61,772	6-Jan-98
rxa02258	900	GB_BA1:CGGAPPGK	3804	X59403	C.glutamicum gap, pgk and tpi genes for glyceraldehyde-3-phosphate, phosphoglycerate kinase and triosephosphate isomerase.	Corynebacterium glutamicum	99,667	05-OCT-1992
		GB_BA1:CORPEPC	4885	M25819	C.glutamicum phosphoenolpyruvate carboxylase gene, complete cds.	Corynebacterium glutamicum	100,000	15-DEC-1995
		GB_PAT:A09073	4885	A09073	C.glutamicum ppg gene for phosphoenol pyruvate carboxylase.	Corynebacterium glutamicum	100,000	25-Aug-93
rxa02259	2895	GB_BA1:CORPEPC	4885	M25819	C.glutamicum phosphoenolpyruvate carboxylase gene, complete cds.	Corynebacterium glutamicum	100,000	15-DEC-1995
		GB_PAT:A09073	4885	A09073	C.glutamicum ppg gene for phosphoenol pyruvate carboxylase.	Corynebacterium glutamicum	100,000	25-Aug-93
		GB_BA1:CGPPC	3292	X14234	Corynebacterium glutamicum phosphoenolpyruvate carboxylase gene (EC 4.1.1.31).	Corynebacterium glutamicum	99,827	12-Sep-93
rxa02288	969	GB_PR3:HSDJ94E24	243145	AL050317	Human DNA sequence from clone RP1-94E24 on chromosome 20q12, complete sequence.	Homo sapiens	36,039	03-DEC-1999
		GB_HTG3:AC010091	159526	AC010091	Homo sapiens clone NH0295A01, *** SEQUENCING IN PROGRESS ***, 4 unordered pieces.	Homo sapiens	35,331	11-Sep-99
		GB_HTG3:AC010091	159526	AC010091	Homo sapiens clone NH0295A01, *** SEQUENCING IN PROGRESS ***, 4 unordered pieces.	Homo sapiens	35,331	11-Sep-99
rxa02292	798	GB_BA2:AF125164	26443	AF125164	Bacteroides fragilis 638R polysaccharide B (PS B2) biosynthesis locus, complete sequence; and unknown genes.	Bacteroides fragilis	39,747	01-DEC-1999
		GB_GSS5:AQ744695	827	AQ744695	HS_5505_A2_C06_SP6 RPCI-11 Human Male BAC Library Homo sapiens genomic clone Plate=1081 Col=12 Row=E, genomic survey sequence.	Homo sapiens	39,185	16-Jul-99
		GB_EST14:AA381925	309	AA381925	EST95058 Activated T-cells I Homo sapiens cDNA 5' end, mRNA sequence.	Homo sapiens	35,922	21-Apr-97
rxa02322	511	GB_BA1:MTCY22G8	22550	Z95585	Mycobacterium tuberculosis H37Rv complete genome; segment 49/162.	Mycobacterium tuberculosis	57,677	17-Jun-98
		GB_BA1:MTCY22G8	22550	Z95585	Mycobacterium tuberculosis H37Rv complete genome; segment 49/162.	Mycobacterium tuberculosis	37,143	17-Jun-98
rxa02326	939	GB_BA1:CGPYC	3728	Y09548	Corynebacterium glutamicum pyc gene.	Corynebacterium glutamicum	100,000	08-MAY-1998
		GB_BA2:AF038548	3637	AF038548	Corynebacterium glutamicum pyruvate carboxylase (pyc) gene, complete cds.	Corynebacterium glutamicum	100,000	24-DEC-1997
		GB_BA1:MTCY349	43523	Z83018	Mycobacterium tuberculosis H37Rv complete genome; segment 131/162.	Mycobacterium tuberculosis	37,363	17-Jun-98
rxa02327	1083	GB_BA1:CGPYC	3728	Y09548	Corynebacterium glutamicum pyc gene.	Corynebacterium glutamicum	99,259	08-MAY-1998
		GB_BA2:AF038548	3637	AF038548	Corynebacterium glutamicum pyruvate carboxylase (pyc) gene, complete cds.	Corynebacterium glutamicum	99,259	24-DEC-1997
		GB_BA1:MTCY349	43523	Z83018	Mycobacterium tuberculosis H37Rv complete genome; segment 131/162.	Mycobacterium tuberculosis	41,317	17-Jun-98

TABLE 4: ALIGNMENT RESULTS

rxa02328	1719	GB_BA1:CGPYC	3728	Y09548	Corynebacterium glutamicum pyc gene.	Corynebacterium glutamicum	100,000	08-MAY-1998
		GB_BA2:AF038548	3637	AF038548	Corynebacterium glutamicum pyruvate carboxylase (pyc) gene, complete cds.	Corynebacterium glutamicum	100,000	24-DEC-1997
		GB_PL2:AF097728	3916	AF097728	Aspergillus terreus pyruvate carboxylase (Pyc) mRNA, complete cds.	Aspergillus terreus	52,248	29-OCT-1998
rxa02332	1266	GB_BA1:MSGLTA	1776	X60513	M.smegmatis gltA gene for citrate synthase.	Mycobacterium smegmatis	58,460	20-Sep-91
		GB_BA2:ABU85944	1334	U85944	Antarctic bacterium DS2-3R citrate synthase (cisy) gene, complete cds.	Antarctic bacterium DS2-3R	57,154	23-Sep-97
		GB_BA2:AE000175	15067	AE000175	Escherichia coli K-12 MG1655 section 65 of 400 of the complete genome.	Escherichia coli	38,164	12-Nov-98
rxa02333	1038	GB_BA1:MSGLTA	1776	X60513	M.smegmatis gltA gene for citrate synthase.	Mycobacterium smegmatis	58,929	20-Sep-91
		GB_PR4:HUAC002299	171681	AC002299	Homo sapiens Chromosome 16 BAC clone CIT987-SKA-113A6 ~complete genomic sequence, complete sequence.	Homo sapiens	33,070	23-Nov-99
		GB_HTG2:AC007889	127840	AC007889	Drosophila melanogaster chromosome 3 clone BACR48E12 (D695) RPCI-98 48.E.12 map 87A-87B strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 86 unordered pieces.	Drosophila melanogaster	34,897	2-Aug-99
rxa02399	1467	GB_BA1:CGACEA	2427	X75504	C.glutamicum aceA gene and thiX genes (partial).	Corynebacterium glutamicum	100,000	9-Sep-94
		GB_BA1:CORACEA	1905	L28760	Corynebacterium glutamicum isocitrate lyase (aceA) gene.	Corynebacterium glutamicum	100,000	10-Feb-95
		GB_PAT:I13693	2135	I13693	Sequence 3 from patent US 5439822.	Unknown.	99,795	26-Sep-95
rxa02404	2340	GB_BA1:CGACEB	3024	X78491	C.glutamicum (ATCC 13032) aceB gene.	Corynebacterium glutamicum	99,914	13-Jan-95
		GB_BA1:CORACEB	2725	L27123	Corynebacterium glutamicum malate synthase (aceB) gene, complete cds.	Corynebacterium glutamicum	99,786	8-Jun-95
		GB_BA1:PFFC2	5588	Y11998	P.fluorescens FC2.1, FC2.2, FC2.3c, FC2.4 and FC2.5c open reading frames.	Pseudomonas fluorescens	63,539	11-Jul-97
rxa02414	870	GB_PR4:AC007102	176258	AC007102	Homo sapiens chromosome 4 clone C0162P16 map 4p16, complete sequence.	Homo sapiens	35,069	2-Jun-99
		GB_HTG3:AC011214	183414	AC011214	Homo sapiens clone 5_C_3, LOW-PASS SEQUENCE SAMPLING.	Homo sapiens	36,885	03-OCT-1999
		GB_HTG3:AC011214	183414	AC011214	Homo sapiens clone 5_C_3, LOW-PASS SEQUENCE SAMPLING.	Homo sapiens	36,885	03-OCT-1999
rxa02435	681	GB_BA2:AF101055	7457	AF101055	Clostridium acetobutylicum atp operon, complete sequence.	Clostridium acetobutylicum	39,605	03-MAR-1999
		GB_OM:RABPKA	4441	J03247	Rabbit phosphorylase kinase (alpha subunit) mRNA, complete cds.	Oryctolagus cuniculus	36,061	27-Apr-93
		GB_OM:RABPLASISM	4458	M64656	Oryctolagus cuniculus phosphorylase kinase alpha subunit mRNA, complete cds.	Oryctolagus cuniculus	36,000	22-Jun-98
rxa02440	963	GB_EST14:AA417723	374	AA417723	zv01b12.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:746207 3' similar to contains Alu repetitive element;contains element L1 repetitive element ;, mRNA sequence.	Homo sapiens	38,770	16-OCT-1997
		GB_EST11:AA215428	303	AA215428	zr95a07.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:683412 3' similar to contains Alu repetitive element;, mRNA sequence.	Homo sapiens	39,934	13-Aug-97
		GB_BA1:MTCY77	22255	Z95389	Mycobacterium tuberculosis H37Rv complete genome; segment 146/162.	Mycobacterium tuberculosis	38,889	18-Jun-98
rxa02453	876	GB_EST14:AA426336	375	AA426336	zv53g02.s1 Soares_testis_NHT Homo sapiens cDNA clone IMAGE:757394 3', mRNA sequence.	Homo sapiens	38,043	16-OCT-1997
		GB_BA1:STMAACC8	1353	M55426	S.fradiae aminoglycoside acetyltransferase (aacC8) gene, complete cds.	Streptomyces fradiae	37,097	05-MAY-1993
		GB_PR3:AC004500	77538	AC004500	Homo sapiens chromosome 5, P1 clone 1076B9 (LBNL H14), complete sequence.	Homo sapiens	33,256	30-MAR-1998
rxa02474	897	GB_BA1:AB009078	2686	AB009078	Brevibacterium saccharolyticum gene for L-2.3-butanediol dehydrogenase, complete cds.	Brevibacterium saccharolyticum	96,990	13-Feb-99
		GB_OM:BTU71200	877	U71200	Bos taurus acetoin reductase mRNA, complete cds.	Bos taurus	51,659	8-Oct-97
		GB_EST2:F12685	287	F12685	HSC3DA031 normalized infant brain cDNA Homo sapiens cDNA clone c-3da03, mRNA sequence	Homo sapiens	41,509	14-Mar-95
rxa02480	1779	GB_BA1:MTV012	70287	AL021287	Mycobacterium tuberculosis H37Rv complete genome; segment 132/162.	Mycobacterium tuberculosis	36,737	23-Jun-99
		GB_BA1:SC6G10	36734	AL049497	Streptomyces coelicolor cosmid 6G10.	Streptomyces coelicolor	35,511	24-MAR-1999
		GB_BA1:AP000060	347800	AP000060	Aeropyrum pernix genomic DNA, section 3/7.	Aeropyrum pernix	48,014	22-Jun-99
rxa02485								

TABLE 4: ALIGNMENT RESULTS

rxa02492	840	GB_BA1:STMPGM	921	M83661	Streptomyces coelicolor phosphoglycerate mutase (PGM) gene, complete cds.	Streptomyces coelicolor	65,672	26-Apr-93
		GB_BA1:MTCY20G9	37218	Z77162	Mycobacterium tuberculosis H37Rv complete genome; segment 25/162.	Mycobacterium tuberculosis	61,436	17-Jun-98
		GB_BA1:U00018	42991	U00018	Mycobacterium leprae cosmid B2168.	Mycobacterium leprae	37,893	01-MAR-1994
rxa02528	1098	GB_PR2:HS161N10	56075	AL008707	Human DNA sequence from PAC 161N10 on chromosome Xq25. Contains EST.	Homo sapiens	37,051	23-Nov-99
		GB_HTG2:AC008235	136017	AC008235	Drosophila melanogaster chromosome 3 clone BACR15B19 (D995) RPCI-98 15.B.19 map 94F-95A strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 125 unordered pieces.	Drosophila melanogaster	36,822	2-Aug-99
		GB_HTG2:AC008235	136017	AC008235	Drosophila melanogaster chromosome 3 clone BACR15B19 (D995) RPCI-98 15.B.19 map 94F-95A strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 125 unordered pieces.	Drosophila melanogaster	36,822	2-Aug-99
rxa02539	1641	GB_BA2:RSU17129	17425	U17129	Rhodococcus erythropolis ThcA (thcA) gene, complete cds; and unknown genes.	Rhodococcus erythropolis	66,117	16-Jul-99
		GB_BA1:MTV038	16094	AL021933	Mycobacterium tuberculosis H37Rv complete genome; segment 24/162.	Mycobacterium tuberculosis	65,174	17-Jun-98
		GB_BA2:AF068264	3152	AF068264	Pseudomonas aeruginosa quinoprotein ethanol dehydrogenase (exaA)gene, partial cds; cytochrome c550 precursor (exaB), NAD+ dependent acetaldehyde dehydrogenase (exaC), and pyrroloquinoline quinone synthesis A (pqqA) genes, complete cds; and pyrroloquinoline quinone synthesis B (pqqB) gene, partial cds.	Pseudomonas aeruginosa	65,448	18-MAR-1999
rxa02551	483	GB_BA1:BACHYPTP	17057	D29985	Bacillus subtilis wapA and orf genes for wall-associated protein and hypothetical proteins.	Bacillus subtilis	53,602	7-Feb-99
		GB_BA1:BACHUTWAPA	28954	D31856	Bacillus subtilis genome containing the hut and wapA loci.	Bacillus subtilis	53,602	7-Feb-99
		GB_BA1:BSGBGLUC	4290	Z34526	B.subtilis (Marburg 168) genes for beta-glucoside permease and beta-glucosidase.	Bacillus subtilis	53,602	3-Jul-95
rxa02556	1281	GB_HTG3:AC008128	335761	AC008128	Homo sapiens, *** SEQUENCING IN PROGRESS ***, 106 unordered pieces.	Homo sapiens	34,022	22-Aug-99
		GB_HTG3:AC008128	335761	AC008128	Homo sapiens, *** SEQUENCING IN PROGRESS ***, 106 unordered pieces.	Homo sapiens	34,022	22-Aug-99
		GB_PL2:AC005292	99053	AC005292	Genomic sequence for Arabidopsis thaliana BAC F26F24, complete sequence.	Arabidopsis thaliana	33,858	16-Apr-99
rxa02560	990	GB_IN1:CEF07A11	35692	Z66511	Caenorhabditis elegans cosmid F07A11, complete sequence.	Caenorhabditis elegans	36,420	2-Sep-99
		GB_EST32:AI731605	566	AI731605	BNLGHi10201 Six-day Cotton fiber Gossypium hirsutum cDNA 5' similar to (AC004684) hypothetical protein [Arabidopsis thaliana], mRNA sequence.	Gossypium hirsutum	38,095	11-Jun-99
		GB_IN1:CEF07A11	35692	Z66511	Caenorhabditis elegans cosmid F07A11, complete sequence.	Caenorhabditis elegans	33,707	2-Sep-99
rxa02572	668	GB_BA1:MTCY63	38900	Z96800	Mycobacterium tuberculosis H37Rv complete genome; segment 16/162.	Mycobacterium tuberculosis	61,677	17-Jun-98
		GB_BA1:MTCY63	38900	Z96800	Mycobacterium tuberculosis H37Rv complete genome; segment 16/162.	Mycobacterium tuberculosis	37,170	17-Jun-98
		GB_HTG1:HS24H01	46989	AL121632	Homo sapiens chromosome 21 clone LLNLc116H0124 map 21q21, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	19,820	29-Sep-99
rxa02596	1326	GB_BA1:MTV026	23740	AL022076	Mycobacterium tuberculosis H37Rv complete genome; segment 157/162.	Mycobacterium tuberculosis	36,957	24-Jun-99
		GB_BA2:AF026540	1778	AF026540	Mycobacterium tuberculosis UDP-galactopyranose mutase (glf) gene, complete cds.	Mycobacterium tuberculosis	67,627	30-OCT-1998
		GB_BA2:MTU96128	1200	U96128	Mycobacterium tuberculosis UDP-galactopyranose mutase (glf) gene, complete cds.	Mycobacterium tuberculosis	70,417	25-MAR-1998
rxa02611	1775	GB_BA1:MTCY130	32514	Z73902	Mycobacterium tuberculosis H37Rv complete genome; segment 59/162.	Mycobacterium tuberculosis	38,532	17-Jun-98
		GB_BA1:MSGY151	37036	AD000018	Mycobacterium tuberculosis sequence from clone y151.	Mycobacterium tuberculosis	60,575	10-DEC-1996
		GB_BA1:U00014	36470	U00014	Mycobacterium leprae cosmid B1549.	Mycobacterium leprae	57,486	29-Sep-94
rxa02612	2316	GB_BA1:MTCY130	32514	Z73902	Mycobacterium tuberculosis H37Rv complete genome; segment 59/162.	Mycobacterium tuberculosis	38,018	17-Jun-98
		GB_BA1:MSGY151	37036	AD000018	Mycobacterium tuberculosis sequence from clone y151.	Mycobacterium tuberculosis	58,510	10-DEC-1996

TABLE 4: ALIGNMENT RESULTS

		GB_BA1:STMGLGEN	2557	L11647	Streptomyces aureofaciens glycogen branching enzyme (glgB) gene, complete cds.	Streptomyces aureofaciens	57,193	25-MAY-1995
rxa02621	942	GB_BA1:CGL133719	1839	AJ133719	Corynebacterium glutamicum yjcc gene, amtR gene and citE gene, partial.	Corynebacterium glutamicum	36,858	12-Aug-99
		GB_IN1:CEM106	39973	Z46935	Caenorhabditis elegans cosmid M106, complete sequence.	Caenorhabditis elegans	37,608	2-Sep-99
		GB_EST29:AI547662	377	AI547662	UI-R-C3-sz-h-03-0-UI.s1 UI-R-C3 Rattus norvegicus cDNA clone UI-R-C3-sz-h-03-0-UI 3', mRNA sequence.	Rattus norvegicus	50,667	3-Jul-99
rxa02640	1650	GB_BA1:MTV025	121125	AL022121	Mycobacterium tuberculosis H37Rv complete genome; segment 155/162.	Mycobacterium tuberculosis	39,187	24-Jun-99
		GB_BA1:PAU49666	4495	U49666	Pseudomonas aeruginosa (orfX), glycerol dfiffusion facilitator (glpF), glycerol kinase (glpK), and Glp repressor (glpR) genes, complete cds, and (orfK) gene, partial cds.	Pseudomonas aeruginosa	59,273	18-MAY-1997
		GB_BA1:AB015974	1641	AB015974	Pseudomonas tolaasii glpK gene for glycerol kinase, complete cds.	Pseudomonas tolaasii	58,339	28-Aug-99
rxa02654	1008	GB_EST6:N65787	512	N65787	20827 Lambda-PRL2 Arabidopsis thaliana cDNA clone 232B7T7, mRNA sequence.	Arabidopsis thaliana	39,637	5-Jan-98
		GB_PL2:T17H3	65839	AC005916	Arabidopsis thaliana chromosome 1 BAC T17H3 sequence, complete sequence.	Arabidopsis thaliana	33,735	5-Aug-99
		GB_RO:MMU58105	88871	U58105	Mus musculus Btk locus, alpha-D-galactosidase A (Ags), ribosomal protein (L44L), and Bruton's tyrosine kinase (Btk) genes, complete cds.	Mus musculus	35,431	13-Feb-97
rxa02666	891	GB_PR3:AC004643	43411	AC004643	Homo sapiens chromosome 16, cosmid clone 363E3 (LANL), complete sequence.	Homo sapiens	38,851	01-MAY-1998
		GB_PR3:AC004643	43411	AC004643	Homo sapiens chromosome 16, cosmid clone 363E3 (LANL), complete sequence.	Homo sapiens	41,599	01-MAY-1998
		GB_BA2:AF049897	9196	AF049897	Corynebacterium glutamicum N-acetylglutamylphosphate reductase (argC), ornithine acetyltransferase (argJ), N-acetylglutamate kinase (argB), acetylornithine transaminase (argD), ornithine carbamoyltransferase (argF), arginine repressor (argR), argininosuccinate synthase (argG), and argininosuccinate lyase (argH) genes, complete cds.	Corynebacterium glutamicum	40,413	1-Jul-98
rxa02675	1980	GB_BA1:PDENQOURF	10425	L02354	Paracoccus denitrificans NADH dehydrogenase (URF4), (NQO8), (NQO9), (URF5), (URF6), (NQO10), (NQO11), (NQO12), (NQO13), and (NQO14) genes, complete cds's; biotin [acetyl-CoA carboxyl] ligase (birA) gene, complete cds.	Paracoccus denitrificans	40,735	20-MAY-1993
		GB_BA1:MTCY339	42861	Z77163	Mycobacterium tuberculosis H37Rv complete genome; segment 101/162.	Mycobacterium tuberculosis	36,471	17-Jun-98
		GB_BA1:MXADEVRS	2452	L19029	Myxococcus xanthus devR and devS genes, complete cds's.	Myxococcus xanthus	38,477	27-Jan-94
rxa02694	1065	GB_BA1:BACLDH	1147	M19394	B.caldolyticus lactate dehydrogenase (LDH) gene, complete cds.	Bacillus caldolyticus	57,371	26-Apr-93
		GB_BA1:BACLDHL	1361	M14788	B.stearothermophilus lct gene encoding L-lactate dehydrogenase, complete cds.	Bacillus stearothermophilus	57,277	26-Apr-93
		GB_PAT:A06664	1350	A06664	B.stearothermophilus lct gene.	Bacillus stearothermophilus	57,277	29-Jul-93
rxa02729	844	GB_EST15:AA494626	121	AA494626	fa09d04.r1 Zebrafish ICRFzfls Danio rerio cDNA clone 11A22 5' similar to TR:G1171163 G1171163 G/T-MISMATCH BINDING PROTEIN. ;, mRNA sequence.	Danio rerio	50,746	27-Jun-97
		GB_EST15:AA494626	121	AA494626	fa09d04.r1 Zebrafish ICRFzfls Danio rerio cDNA clone 11A22 5' similar to TR:G1171163 G1171163 G/T-MISMATCH BINDING PROTEIN. ;, mRNA sequence.	Danio rerio	36,364	27-Jun-97
rxa02730	1161	GB_EST19:AA758660	233	AA758660	ah67d06.s1 Soares_testis_NHT Homo sapiens cDNA clone 1320683 3', mRNA sequence.	Homo sapiens	37,059	29-DEC-1998
		GB_EST15:AA494626	121	AA494626	fa09d04.r1 Zebrafish ICRFzfls Danio rerio cDNA clone 11A22 5' similar to TR:G1171163 G1171163 G/T-MISMATCH BINDING PROTEIN. ;, mRNA sequence.	Danio rerio	42,149	27-Jun-97

TABLE 4: ALIGNMENT RESULTS

		GB_PR4:AC006285	150172	AC006285	Homo sapiens, complete sequence.	Homo sapiens	37,655	15-Nov-99
rxa02737	1665	GB_PAT:E13655	2260	E13655	gDNA encoding glucose-6-phosphate dehydrogenase.	Corynebacterium glutamicum	99,580	24-Jun-98
		GB_BA1:MTCY493	40790	Z95844	Mycobacterium tuberculosis H37Rv complete genome; segment 63/162.	Mycobacterium tuberculosis	38,363	19-Jun-98
		GB_BA1:SC5A7	40337	AL031107	Streptomyces coelicolor cosmid 5A7.	Streptomyces coelicolor	39,444	27-Jul-98
rxa02738	1203	GB_PAT:E13655	2260	E13655	gDNA encoding glucose-6-phosphate dehydrogenase.	Corynebacterium glutamicum	98,226	24-Jun-98
		GB_BA1:SCC22	22115	AL096839	Streptomyces coelicolor cosmid C22.	Streptomyces coelicolor	60,399	12-Jul-99
		GB_BA1:SC5A7	40337	AL031107	Streptomyces coelicolor cosmid 5A7.	Streptomyces coelicolor	36,426	27-Jul-98
rxa02739	2223	GB_BA1:AB023377	2572	AB023377	Corynebacterium glutamicum tkt gene for transketolase, complete cds.	Corynebacterium glutamicum	99,640	20-Feb-99
		GB_BA1:MLCL536	36224	Z99125	Mycobacterium leprae cosmid L536.	Mycobacterium leprae	61,573	04-DEC-1998
		GB_BA1:U00013	35881	U00013	Mycobacterium leprae cosmid B1496.	Mycobacterium leprae	61,573	01-MAR-1994
rxa02740	1053	GB_HTG2:AC006247	174368	AC006247	Drosophila melanogaster chromosome 2 clone BACR48I10 (D505) RPCI-98 48.I.10 map 49E6-49F8 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 17 unordered pieces.	Drosophila melanogaster	37,105	2-Aug-99
		GB_HTG2:AC006247	174368	AC006247	Drosophila melanogaster chromosome 2 clone BACR48I10 (D505) RPCI-98 48.I.10 map 49E6-49F8 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 17 unordered pieces.	Drosophila melanogaster	37,105	2-Aug-99
		GB_HTG3:AC007150	121474	AC007150	Drosophila melanogaster chromosome 2 clone BACR16P13 (D597) RPCI-98 16.P.13 map 49E-49F strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, 87 unordered pieces.	Drosophila melanogaster	38,728	20-Sep-99
rxa02741	1089	GB_HTG2:AC004951	129429	AC004951	Homo sapiens clone DJ1022I14, *** SEQUENCING IN PROGRESS ***, 14 unordered pieces.	Homo sapiens	33,116	12-Jun-98
		GB_HTG2:AC004951	129429	AC004951	Homo sapiens clone DJ1022I14, *** SEQUENCING IN PROGRESS ***, 14 unordered pieces.	Homo sapiens	33,116	12-Jun-98
		GB_IN1:AB006546	931	AB006546	Ephydatia fluviatilis mRNA for G protein a subunit 4, partial cds.	Ephydatia fluviatilis	36,379	23-Jun-99
rxa02743	1161	GB_BA1:MLCL536	36224	Z99125	Mycobacterium leprae cosmid L536.	Mycobacterium leprae	48,401	04-DEC-1998
		GB_BA1:U00013	35881	U00013	Mycobacterium leprae cosmid B1496.	Mycobacterium leprae	48,401	01-MAR-1994
		GB_HTG2:AC007401	83657	AC007401	Homo sapiens clone NH0501O07, *** SEQUENCING IN PROGRESS ***, 3 unordered pieces.	Homo sapiens	37,128	26-Jun-99
rxa02797	1026	GB_BA1:CGBETPGEN	2339	X93514	C.glutamicum betP gene.	Corynebacterium glutamicum	38,889	8-Sep-97
		GB_GSS9:AQ148714	405	AQ148714	HS_3136_A1_A03_MR CIT Approved Human Genomic Sperm Library D Homo sapiens genomic clone Plate=3136 Col=5 Row=A, genomic survey sequence.	Homo sapiens	34,321	08-OCT-1998
		GB_BA1:BFU64514	3837	U64514	Bacillus firmus dppABC operon, dipeptide transporter protein dppA gene, partial cds, and dipeptide transporter proteins dppB and dppC genes, complete cds.	Bacillus firmus	38,072	1-Feb-97
rxa02803	680	GB_BA1:U00020	36947	U00020	Mycobacterium leprae cosmid B229.	Mycobacterium leprae	34,462	01-MAR-1994
		GB_BA2:PSU85643	4032	U85643	Pseudomonas syringae pv. syringae putative dihydropteroate synthase gene, partial cds, regulatory protein MrsA (mrsA), triose phosphate isomerase (tpiA), transport protein SecG (secG), tRNA-Leu, tRNA-Met, and 15 kDa protein genes, complete cds.	Pseudomonas syringae pv. syringae	50,445	9-Apr-97
		GB_BA1:SC6G4	41055	AL031317	Streptomyces coelicolor cosmid 6G4.	Streptomyces coelicolor	59,314	20-Aug-98
rxa02821	363	GB_HTG2:AC008105	91421	AC008105	Homo sapiens chromosome 17 clone 2020_K_17 map 17, *** SEQUENCING IN PROGRESS ***, 12 unordered pieces.	Homo sapiens	37,607	22-Jul-99
		GB_HTG2:AC008105	91421	AC008105	Homo sapiens chromosome 17 clone 2020_K_17 map 17, *** SEQUENCING IN PROGRESS ***, 12 unordered pieces.	Homo sapiens	37,607	22-Jul-99
		GB_EST33:AV117143	222	AV117143	AV117143 Mus musculus C57BL/6J 10-day embryo Mus musculus cDNA clone 2610200J17, mRNA sequence.	Mus musculus	40,157	30-Jun-99

TABLE 4: ALIGNMENT RESULTS

rxa02829	373	GB_HTG1:HSU9G8	48735	AL008714	Homo sapiens chromosome X clone LL0XNC01-9G8, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	41,595	23-Nov-99
		GB_HTG1:HSU9G8	48735	AL008714	Homo sapiens chromosome X clone LL0XNC01-9G8, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	41,595	23-Nov-99
		GB_PR3:HSU85B5	39550	Z69724	Human DNA sequence from cosmid U85B5, between markers DXS366 and DXS87 on chromosome X.	Homo sapiens	41,595	23-Nov-99
rxc03216	1141	GB_HTG3:AC008184	151720	AC008184	Drosophila melanogaster chromosome 2 clone BACR04D05 (D540) RPCI-98 04.D.5 map 36E5-36F2 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ***, 27 unordered pieces.	Drosophila melanogaster	39,600	2-Aug-99
		GB_EST15:AA477537	411	AA477537	zu36g12.r1 Soares ovary tumor NbHOT Homo sapiens cDNA clone IMAGE:740134 5' similar to contains Alu repetitive element;contains element HGR repetitive element ;, mRNA sequence.	Homo sapiens	37,260	9-Nov-97
		GB_EST26:AI330662	412	AI330662	fa91d08.y1 zebrafish fin day1 regeneration Danio rerio cDNA 5', mRNA sequence.	Danio rerio	37,805	28-DEC-1998
rxs03215	1038	GB_BA1:SC3F9	19830	AL023862	Streptomyces coelicolor cosmid 3F9.	Streptomyces coelicolor A3(2)	48,657	10-Feb-99
		GB_BA1:SLLINC	36270	X79146	S.lincolnensis (78-11) Lincomycin production genes.	Streptomyces lincolnensis	39,430	15-MAY-1996
		GB_HTG5:AC009660	204320	AC009660	Homo sapiens chromosome 15 clone RP11-424J10 map 15, *** SEQUENCING IN PROGRESS ***, 41 unordered pieces.	Homo sapiens	35,151	04-DEC-1999
rxs03224	1288	GB_PR3:AC004076	41322	AC004076	Homo sapiens chromosome 19, cosmid R30217, complete sequence.	Homo sapiens	37,788	29-Jan-98
		GB_PL2:SPAC926	23193	AL110469	S.pombe chromosome I cosmid c926.	Schizosaccharomyces pombe	38,474	2-Sep-99
		GB_BA2:AE001081	11473	AE001081	Archaeoglobus fulgidus section 26 of 172 of the complete genome.	Archaeoglobus fulgidus	35,871	15-DEC-1997